22096

PC[illegible]

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

[illegible]ceiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 14704 KB

Box No. I TITLE OF INVENTION

NEW 2,3-BENZODIAZEPINE DERIVATIVES

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

EGIS GYÓGYSZERGYÁR RT.
Budapest, Keresztúri út 30-38., H-1106
Hungary

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

GREFF, Zoltán
Budapest, Gyöngyvirág u. 8., H-1028
Hungary

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ADVOPATENT Office of Patent and Trademark Attorneys
Budapest, P.O.Box 11, H-1251
Hungary

Telephone No. (36-1) 201-1528

Facsimile No. (36-1) 201-1692

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SZABÓ, Géza
Budapest, Hold u. 25., H-1054
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BARKÓCZY, József
Budapest, Szirom u. 4-6/B, H-1016
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

RÁTKAI, Zoltán
Budapest, Monori u. 19., H-1101
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BLASKÓ, Gábor
Budapest, Pósa Lajos u. 41., H-1149
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

[X] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SIMIG, Gyula
Budapest, Hollósy Simon u. 25., H-1126
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

GIGLER, Gábor
Budapest, Etele út 73., H-1119
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MARTONNÉ MARKÓ, Bernadett
Budapest, Pásztorfalva u. 14., H-1171
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LÉVAY, György
Budakeszi, Gábor Áron u. 10., H-2092
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

[X] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

TIHANYI, Károly
Budapest, Postamester u. 37., H-1171
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

EGYED, András
Budapest, Újvidék u. 58., H-1145
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SIMÓ, Annamária
Budapest, Radnóti M. u. 24., H-1137
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

- [ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ AP **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ EP **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ AE United Arab Emirates
☒ AL Albania
☒ AM Armenia
☒ AT Austria
☒ AU Australia
☒ AZ Azerbaijan
☒ BA Bosnia and Herzegovina
☒ BB Barbados
☒ BG Bulgaria
☒ BR Brazil
☒ BY Belarus
☒ CA Canada
☒ CH and LI Switzerland and Liechtenstein
☒ CN China
☒ CR Costa Rica
☒ CU Cuba
☒ CZ Czech Republic
☒ DE Germany
☒ DK Denmark
☒ DM Dominica
☒ EE Estonia
☒ ES Spain
☒ FI Finland
☒ GB United Kingdom
☒ GD Grenada
☒ GE Georgia
☒ GH Ghana
☒ GM Gambia
☒ HR Croatia
☐ HU Hungary
☒ ID Indonesia
☒ IL Israel
☒ IN India
☒ IS Iceland
☒ JP Japan
☒ KE Kenya
☒ KG Kyrgyzstan
☒ KP Democratic People's Republic of Korea
☒ KR Republic of Korea
☒ KZ Kazakhstan
☒ LC Saint Lucia
☒ LK Sri Lanka
☒ LR Liberia
☒ LS Lesotho
☒ LT Lithuania
☒ LU Luxembourg
☒ LV Latvia
☒ MA Morocco
☒ MD Republic of Moldova
☒ MG Madagascar
☒ MK The former Yugoslav Republic of Macedonia
☒ MN Mongolia
☒ MW Malawi
☒ MX Mexico
☒ NO Norway
☒ NZ New Zealand
☒ PL Poland
☒ PT Portugal
☒ RO Romania
☒ RU Russian Federation
☒ SD Sudan
☒ SE Sweden
☒ SG Singapore
☒ SI Slovenia
☒ SK Slovakia
☒ SL Sierra Leone
☒ TJ Tajikistan
☒ TM Turkmenistan
☒ TR Turkey
☒ TT Trinidad and Tobago
☒ TZ United Republic of Tanzania
☒ UA Ukraine
☒ UG Uganda
☒ US United States of America
☒ UZ Uzbekistan
☒ VN Viet Nam
☒ YU Yugoslavia
☒ ZA South Africa
☒ ZW Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ AG Antigua and Bermuda
☒ BZ Belize
☒ DZ Algeria
☒ MZ Mozambique

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLA[illegible] ☐ Further priorit[illegible]ns are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 07/July/1999 (07/07/99)	P9902291	Hungary		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*
ISA/

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*
Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request	6
description (excluding sequence listing part)	61
claims	17
abstract	2
drawings	
sequence listing part of description	
Total number of sheets	89

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

KARÁCSONYI, Béla
Patent Attorney

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA/
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET
Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: 14704 KB

Applicant: EGIS GYOGYSZERGYÁR RT. et al.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . HUF . . . 18 500.- [T]

2. SEARCH FEE . . . . . EUR . . . 945.- [S]

International search to be carried out by: EP

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 89 sheets.

first 30 sheets . . . . . CHF . . 650.- [b1]

59 (remaining sheets) x 15 (additional amount) CHF = 885.- [b2]

Add amounts entered at b1 and b2 and enter total at B . CHF . 1535.- [B]

Designation Fees

The international application contains all designations.

_____ (number of designation fees payable *(maximum 8)*) x _____ CHF (amount of designation fee) = 1120.- [D]

Add amounts entered at B and D and enter total at I . . . . . CHF 2655.- [I]

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . [P]

5. TOTAL FEES PAYABLE . . . . . [TOTAL]

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

[X] The designation fees are not paid at this time.

MODE OF PAYMENT

- [ ] authorization to charge deposit account (see below)
- [X] bank draft
- [ ] coupons
- [ ] cheque
- [ ] cash
- [ ] other *(specify)*:
- [ ] postal money order
- [ ] revenue stamps

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ _____

- [ ] is hereby authorized to charge the total fees indicated above to my deposit account.
- [ ] *(this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.
- [ ] is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

Deposit Account No. | Date *(day/month/year)* | Signature

See Notes to the fee calculation sheet

20096

PATENT COOPERATION TREA

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
ADVOPATENT Office of Patent and Trademark Attorneys
P.O. Box 11
H-1251 Budapest
HUNGARY

	Date of mailing *(day/month/year)* 30/01/2001
Applicant's or agent's file reference 14704 KB	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/HU 00/ 00074	International filing date *(day/month/year)* 04/07/2000
Applicant EGIS GYOGYSZERGYAR RT. et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Maurizio Amodeo

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the International application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
14704 KB		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/HU 00/ 00074	04/07/2000	07/07/1999
Applicant		
EGIS GYOGYSZERGYAR RT. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. ---

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 00/00074

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D491/04 A61K31/551 A61P25/00 //(C07D491/04,317:00, 243:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 07707 A (EGIS GYOGYSZERGYAR RT) 18 February 1999 (1999-02-18) the whole document	1-27
Y	WO 92 11262 A (GYOGYSRERKUTATO INTEZET K.V.) 9 July 1992 (1992-07-09) the whole document	1-27
Y	WO 97 34878 A (COCENSYS, INC.) 25 September 1997 (1997-09-25) the whole document	1-27
Y	EP 0 492 485 A (GYOGYSZERKUTATO INTEZET) 1 July 1992 (1992-07-01) the whole document	1-27

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2001	30/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Beslier, L

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 00/00074

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 01357 A (GYOGYSZERKUTATO INTEZET KFT.) 12 January 1995 (1995-01-12) the whole document	1-27

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 00/00074

Box I Observations wher certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 27 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU 00/00074

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9907707 A	18-02-1999	HU 9701380 A	28-06-1999
		HU 9701381 A	28-06-1999
		AU 8818198 A	01-03-1999
		CN 1272846 T	08-11-2000
		EP 1003749 A	31-05-2000
		NO 20000655 A	10-04-2000
		PL 338680 A	20-11-2000
WO 9211262 A	09-07-1992	HU 59683 A	29-06-1992
		AU 9122691 A	22-07-1992
		CA 2098291 A	22-06-1992
		EP 0565557 A	20-10-1993
		JP 6506442 T	21-07-1994
WO 9734878 A	25-09-1997	AU 2527097 A	10-10-1997
		EP 1021418 A	26-07-2000
		JP 2000506890 T	06-06-2000
		US 5891871 A	06-04-1999
EP 492485 A	01-07-1992	HU 59684 A	29-06-1992
		US 5459137 A	17-10-1995
		AT 160350 T	15-12-1997
		AU 641578 B	23-09-1993
		AU 8996391 A	25-06-1992
		BR 9105517 A	01-09-1992
		CA 2057504 A	22-06-1992
		CN 1062730 A,B	15-07-1992
		CN 1191111 A	26-08-1998
		CZ 9103985 A	19-01-1994
		DE 69128236 D	02-01-1998
		DE 69128236 T	14-05-1998
		DK 492485 T	27-07-1998
		ES 2112848 T	16-04-1998
		FI 916032 A	22-06-1992
		GR 3026127 T	29-05-1998
		HR 920677 A	31-08-1994
		IL 100449 A	31-12-1995
		JP 2756742 B	25-05-1998
		JP 5070463 A	23-03-1993
		KR 169134 B	15-01-1999
		MX 9102734 A	01-06-1992
		NO 300376 B	20-05-1997
		NZ 241110 A	27-04-1994
		SI 9111966 A	30-04-1998
		RU 2102387 C	20-01-1998
		US 5604223 A	18-02-1997
		US 5536832 A	16-07-1996
		US 5519019 A	21-05-1996
		US 5521174 A	28-05-1996
		US 5639751 A	17-06-1997
		ZA 9110064 A	28-10-1992
WO 9501357 A	12-01-1995	HU 67611 A	28-04-1995
		AU 7236394 A	24-01-1995

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

28096

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 14704 KB

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/HU00/00074	04 July 2000 (04.07.00)	07 July 1999 (07.07.99)

Title of invention
NEW 2,3-BENZODIAZEPINE DERIVATIVES

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
EGIS GYÓGYSZERGYÁR RT.
Budapest, Keresztúri út 30-38., H-1106
Hungary

Telephone No.:

Facsimile No.:

Teleprinter No.:

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
GREFF, Zoltán
Budapest, Gyöngyvirág u. 8., H-1028
Hungary

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
SZABÓ, Géza
Budapest, Hold u. 25., H-1054
Hungary

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

[X] Further applicants are indicated on a continuation sheet.

International application No.
PCT/HU00/00074

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BARKÓCZY, József
Budapest, Szirom u. 4-6/B, H-1016
Hungary

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RÁTKAI, Zoltán
Budapest, Menori u. 19., H-1101
Hungary

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BLASKÓ, Gábor
Budapest, Pósa Lajos u. 41., H-1149
Hungary

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SIMIG, Gyula
Budapest, Hollósy Simon u. 25., H-1126
Hungary

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

[X] Further applicants are indicated on another continuation sheet.

International application No.
PCT/HU00/00074

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GIGLER, Gábor
Budapest, Etele út 73., H-1119
Hungary

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Hungary	Hungary

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MARTONNÉ MARKÓ, Bernadett
Budapest, Pásztorfalva u. 14., H-1171
Hungary

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Hungary	Hungary

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LÉVAY, György
Budakeszi, Gábor Áron u. 10., H-2092
Hungary

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Hungary	Hungary

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

TIHANYI, Károly
Budapest, Postamester u. 37., H-1171
Hungary

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Hungary	Hungary

[X] Further applicants are indicated on another continuation sheet.

Sheet No. 4

International application No.
PCT/HU00/00074

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

EGYED, András
Budapest, Újvidék u. 58., H-1145
Hungary

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Hungary	Hungary

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SIMÓ, Annamária
Budapest, Radnóti M. u. 24., H-1137
Hungary

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Hungary	Hungary

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/HU00/00074

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ADVOPATENT Office of Patent and Trademark Attorneys
Budapest, P.O.Box 11, H-1251
Hungary

Telephone No.: (36-1) 201-1528

Facsimile No.: (36-1) 201-1692

Teleprinter No.:

[ ] Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination **to start on the basis of:**

[X] the international application as originally filed

the description [X] as originally filed
[ ] as amended under Article 34

the claims [X] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings [X] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

[X] which is the language in which the international application was filed.
[ ] which is the language of a translation furnished for the purposes of international search.
[ ] which is the language of publication of the international application.
[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects **all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes **not to elect:**

Sheet No. 6.

International application No.
PCT/HU00/00074

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. [X] fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ nucleotide and or amino acid sequence listing in computer readable form
6. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

(KARÁCSONYI, Béla)
Patent Attorney

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

See Notes to the demand form

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. PCT/HU00/00074	For International Preliminary Examining Authority use only
Applicant's or agent's file reference 14704 KB	Date stamp of the IPEA

Applicant EGIS GYÓGYSZERGYÁR RT. et al.

Calculation of prescribed fees

1. Preliminary examination fee	EUR	1533.-	P
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	EUR	147.-	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EUR	1680.- TOTAL	

Mode of Payment

☐	authorization to charge deposit account with the IPEA (see below)	☐	cash
☐	cheque	☐	revenue stamps
☐	postal money order	☐	coupons
☒	bank draft	☐	other *(specify)*:

Deposit Account Authorization *(this mode of payment may not be available at all IPEAs)*

The IPEA/ _____ ☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☐ *(this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

Deposit Account Number	Date *(day/month/year)*	Signature

22096

2000 NOV 27

PCT/HU00/0007

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

ADVOPATENT
P.O. Box 11
H-1251 Budapest
HONGRIE

Date of mailing (day/month/year) 17 November 2000 (17.11.00)	
Applicant's or agent's file reference 14704 KB	**IMPORTANT NOTIFICATION**
International application No. PCT/HU00/00074	International filing date (day/month/year) 04 July 2000 (04.07.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 07 July 1999 (07.07.99)
Applicant EGIS GYÓGYSZERGYÁR RT. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
07 July 1999 (07.07.99)	P 9902291	HU	27 Sept 2000 (27.09.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Henrik Nyberg

Telephone No. (41-22) 338.83.38

63333

14

PATENT COOPERATION TREATY

PCT

REC'D 07 AUG 2001

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
14704 KB		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/HU00/00074	04/07/2000	07/07/1999
International Patent Classification (IPC) or national classification and IPC C07D491/04		
Applicant EGIS GYOGYSZERGYAR RT. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26/01/2001	03.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stroeter, T Telephone No. +49 89 2399 8088

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/HU00/00074

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1,2,4-28,30-61	as originally filed			
3,3a-3c,29	as received on	28/06/2001	with letter of	27/06/2001

Claims, No.:

1 (part),7 (part), 8-20,21 (part)	as originally filed			
1 (part),2-6,7 (part), 21 (part),22-27	as received on	28/06/2001	with letter of	27/06/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 27.

because:

   ☒ the said international application, or the said claims Nos. 27 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-26
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 27 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Prior art documents

Reference is made to the following documents which mention 1,3-dioxolo-2,3-benzodiazepine derivatives. The given numbering will be adhered to in the rest of the procedure:

D1: WO 99 07707 A (EGIS GYOGYSZERGYAR RT)
D2: WO 92 11262 A (GYOGYSRERKUTATO INTEZET K.V.)
D3: WO 97 34878 A (COCENSYS, INC.)
D4: EP-A-0 492 485 (GYOGYSZERKUTATO INTEZET)
D5: WO 95 01357 A (GYOGYSZERKUTATO INTEZET KFT.)

2 Novelty (Article 33(2) PCT) and Inventive step (Article 33(3) PCT)

Article 33(2) PCT: The group of compounds as claimed in present claim 1 (as well as in dependent claims 2 to 11) is novel over the compounds disclosed in D1 to D5 due to the presence of a methyl group in 3-position (and as such in o-position to the amino group or NO_2 group, respectively) of the phenyl ring.

Article 33(3) PCT: Document D4 names in examples 15-25 some structurally related neuroprotective agents which (partly) act according to D2, page 4, 2nd paragraph, as antagonists of AMPA receptors.

By revealing the present compounds of formula (I), the present application gives a non-obvious solution to the problem of how to provide AMPA receptor antagonists having an improved neuroprotective activity, i.e. a lower PD_{50} value compared to the closest prior art compounds of D4. The presence of the methyl group as stated above leads to a slower N-acetylation of the neighbouring amino group (this reaction is an undesired metabolic effect since it leads to less active compounds) as was made credible via the comparative data given on present pages 28-30. As a consequence the sterically hindered compounds have a better neuroprotective effect than those having no methyl group in 3-position as shown in the table on present page 32. Thus, the presently claimed compounds have an advantageous effect over the closest prior art compounds and are therefore involving an inventive step.

Consequently, present claims 1-11 and claims 12-27 which refer directly or indirectly to the compounds of present formula I are novel and inventive according to Articles 33(2) and (3) PCT.

3 Industrial applicability (Article 33(4) PCT)

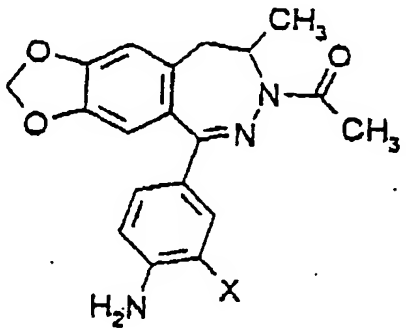
The subject-matter of the present claims 1 to 26 is in accordance with the requirements of Article 33(4) PCT.

For the assessment of the present **claim 27** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The therapeutical use of 2,3-benzodiazepines which exhibit a non-competitive antagonist effect on the AMPA/cainate receptor is manifold. The 2,3-benzodiazepines synthetized by research chemists of our company can be used as neuroprotective agents in case of symptoms accompanied by all types of acute and chronical neurodegeneration (e.g. Parkinson disease, Alzheimer disease, amyotropic lateral sclerosis, stroke, acute head injuries etc.). In addition to the above applications 2,3--benzodiazepines having AMPA/cainate antagonistic effect can also be used for the treatment of further symptoms, such as epilepsy, as spasmolytics, analgesics, antiemetic agents, against schizophreny, migraine, urination problems, as anxiolytics, against drug addiction, to alleviate the symptoms of Parkinsonism etc. [I. Tarnawa and E. S. Vizi, Restorative Neurol. Neurosci. 13, 41-57, (1998)].

The following references of prior art compounds A to F are listed:

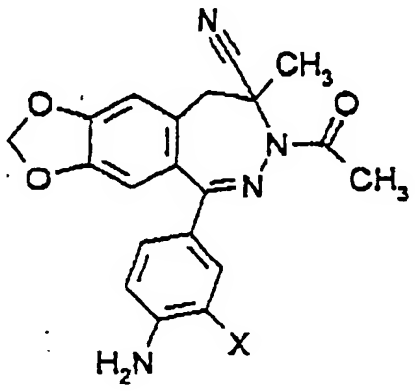
Compound A X = H



Vizi, E.S., Mike, A., Tamawa, I.: 2,3-Benzodiazepines (GYKI-52466 and analogs): negative allosteric modulators of AMPA receptors. CNS Drug Reviews, 1996, 2, 91-126.

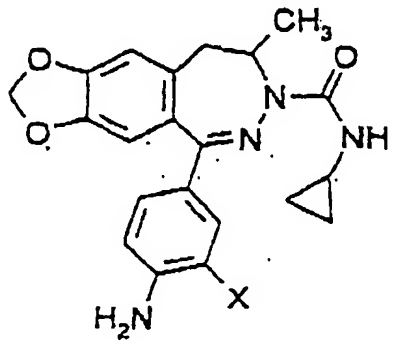
Tamawa, I., Vizi, E. S.: 2,3-Benzodiazepine AMPA antagonists. Restorative Neurology and Neuroscience, 1998, 13, 41-57.

Compound B X = H



PCT WO 99/07707, 08/07/1998.

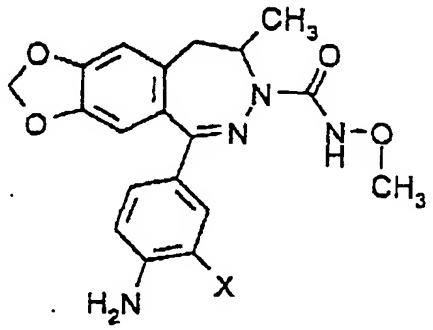
Compound C X = H



PCT WO 99/07708, 08/07/1998

Levay, G., Simo, A., Barkoczy, J., Tihanyi, K., Vegh, M., Gigler, G.: EGIS-9637, a novel antiischaemic drug exerts complex neuroprotective properties. Soc. Neurosci. Abstr. 234.13., 1999.

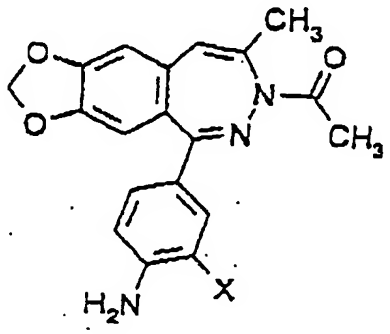
Compound D X = H



Vizi, E. S., Mike, A., Tarnawa, I.: 2,3-Benzodiazepines (GYKI-52466 and analogs): negative allosteric modulators of AMPA receptors. CNS Drug Reviews, 1996, 2, 91-126.

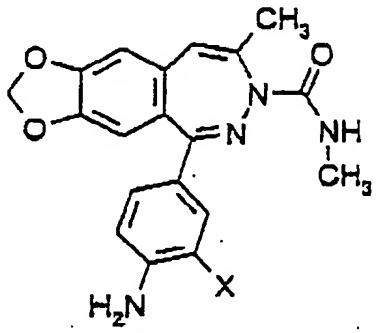
Tarnawa, I., Vizi, E.S.: 2,3-Benzodiazepine AMPA antagonists. Restorative Neurology and Neuroscience, 1998, 13, 41-57.

Compound E X = H



PCT WO 9604283A1, 07/28/1995

Compound F X = H



PCT WO 9604283A1, 07/28/1995

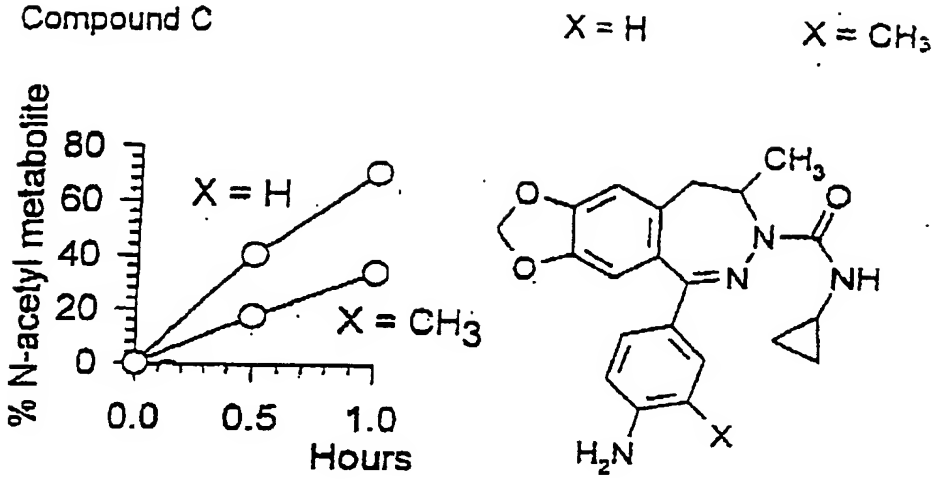
DESCRIPTION OF THE INVENTION

It is the object of the present invention to provide new 2,3-benzodiazepine derivatives having favourable biological properties.

The above object is solved by the present invention.

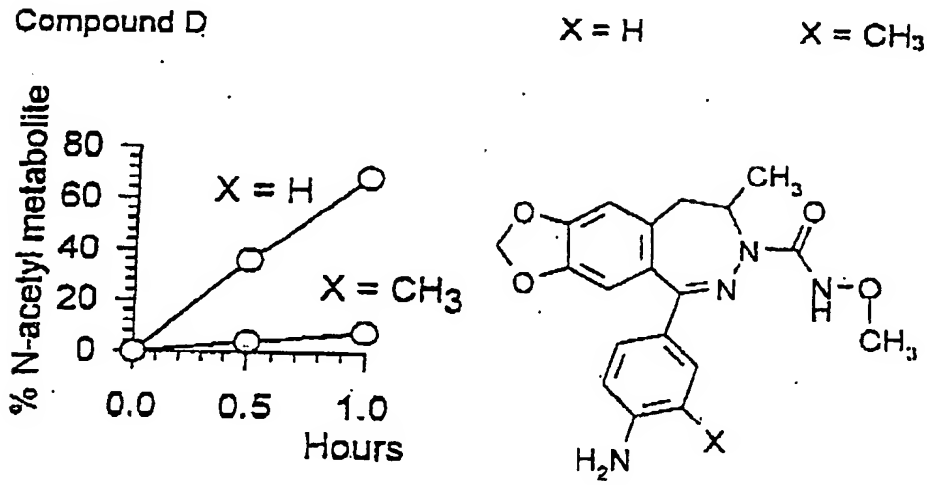
According to the present invention there are provided new compounds of the general Formula

Compound C



(Example 29)

Compound D



(Example 30)

heterocyclic ring optionally containing one or more further nitrogen, sulfur and/or oxygen atom(s);

R^4 is hydrogen or lower alkyl;

the dotted lines have the following meaning:

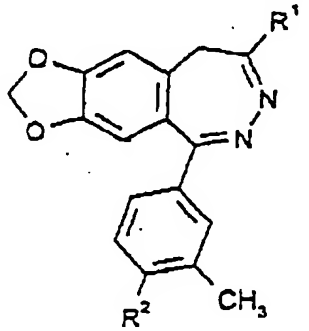
if R^3 and R^4 are not present, the bond between positions C^8 and C^9 is a single bond and the bond between positions C^8 and N^7 is a double bond;

if R^3 and R^4 are present, the bonds between positions C^8 and C^9 and between positions C^8 and N^7 are single bonds; and

if R^3 is present and R^4 is missing, the bond between positions C^8 and C^9 is a double bond and the bond between positions C^8 and N^7 is a single bond)

and pharmaceutically acceptable salts thereof.

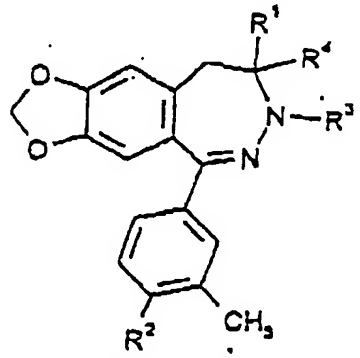
2. Compounds according to claim 1 of the general Formula



IA

(wherein R^1 and R^2 are as stated in Claim 1) and pharmaceutically acceptable acid addition salts thereof.

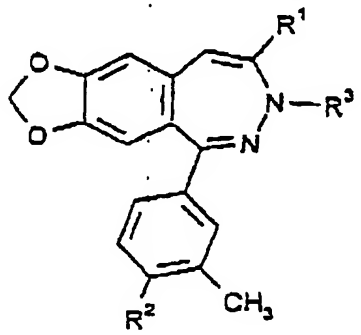
3. Compounds according to claim 1 of the general Formula



IB

(wherein R^1, R^2, R^3 and R^4 are as stated in Claim 1) and pharmaceutically acceptable acid addition salts thereof.

4. Compounds according to claim 1 of the general Formula



IC

(wherein R^1, R^2 and R^3 are as stated in Claim 1) and pharmaceutically acceptable acid addition salts thereof.

5. Compounds according to any of Claims 1-4 wherein R^2 is amino.

6. Compounds of the general Formula IB according to Claim 5.

7. Compounds according to Claim 6 wherein R^1 stands for methyl or cyano; R^2 is amino; R^3 represents lower alkanoyl or -$CONR^7R^8$; R^7 is hydrogen; R^8 is lower alkyl, lower

-phenyl)-7-propionyl-7,8-dihydro-8-methyl-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-(N-cyclopropyl-carbamoyl)-7,8--dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-(N-methoxy-carbamoyl)-7,8--dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-(N-methyl-carbamoyl)-7,8--dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-acetyl-8-cyano-7,8-dihydro-8--methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-8-cyano-7-propionyl-7,8-dihydro--8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine.

22. Pharmaceutical composition according to Claim 16 which comprises as active ingredient a compound of the general Formula IC wherein R^1 is methyl; R^2 stands for amino; R^3 is lower alkanoyl or -CO-NR^7R^8; R^7 is hydrogen and R^8 represents lower alkyl, lower alkoxy or lower cycloalkyl.

23. Pharmaceutical composition according to Claim 22 which comprises as active ingredient
7-acetyl-5-(4-amino-3-methyl-phenyl)-8-methyl-7H-1,3--dioxolo[4,5-h][2,3]benzodiazepine;
7-(N-methyl-carbamoyl)- 5-(4-amino-3-methyl-phenyl)-8--methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
7-(N-cyclopropyl-carbamoyl)- 5-(4-amino-3-methyl-phenyl)-8--methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine.

24. Pharmaceutical compositions according to claim 16 containing as active ingredient a compound of the general

Formula I as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof having neuroprotective effect, useful in the treatment of symptoms accompanied by all kinds of acute and chronical neurodegeneration, especially Parkinson disease, Alzheimer disease, amyotropic lateral sclerosis, stroke, acute head injuries, epilepsy, against spasms, alleviation of pain, to influence vomitting, schisophreny, migraine, urination problems, as anxyolitics, against drug addiction and to alleviate the symptoms of Parkinsonism.

25. Process for the preparation of pharmaceutical compositions according to Claims 16-23 which comprises admixing a compound of the general Formula I or a pharmaceutically acceptable acid addition salt thereof with inert solid or liquid pharmaceutical carriers and bringing the mixture to a galenic form.

26. Use of compounds of the general Formula I and pharmaceutically acceptable acid addition salts thereof for the preparation of pharmaceutical compositions having neuroprotective effect, useful in the treatment of symptoms accompanied by all kinds of acute and chronical neurodegeneration, especially Parkinson disease, Alzheimer disease, amyotropic lateral sclerosis, stroke, acute head injuries, epilepsy, against spasms, alleviation of pain, to influence vomitting, schisophreny, migraine, urination problems, as anxyolitics, against drug addiction and to alleviate the symptoms of Parkinsonism.

27. Method of treatment of symptoms accompanied by all kinds of acute and chronical neurodegeneration, especially Parkinson disease, Alzheimer disease, amyotropic lateral sclerosis, stroke, acute head injuries, epilepsy, against spasms, alleviation of pain, to influence vomitting, schisophreny, migraine, urination problems, as anxyolitics, against drug addiction and to alleviate the symptoms of Parkinsonism, which comprises administering to a patient in need of such treatment a pharmaceutically effective amount of a compound of the general Formula I or a pharmaceutically acceptable acid addition salt thereof.

— • —

PATENT COOPERATION TI .TY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 30 March 2001 (30.03.01)	
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International filing date (day/month/year) 04 July 2000 (04.07.00)	**Priority date** (day/month/year) 07 July 1999 (07.07.99)
Applicant GREFF, Zoltán et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

26 January 2001 (26.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer H. Zhou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

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(71) Applicant *(for all designated States except US)*: **EGIS GYÓGYSZERGYÁR RT.** [HU/HU]; Keresztúri út 30-38, H-1106 Budapest (HU).

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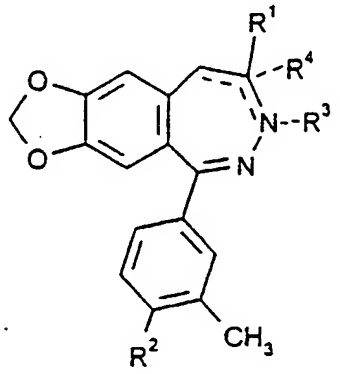
(74) Agent: **ADVOPATENT**; Office of Patent and Trademark Attorneys, P.O. Box 11, H-1251 Budapest (HU).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian

[Continued on next page]

(54) Title: NEW 2,3-BENZODIAZEPINE DERIVATIVES



(I)

(57) Abstract: The invention relates to new 2,3-benzodiazepine derivatives of general Formula (I), (wherein R^1 stands for methyl, formyl, carboxy, cyano, -CH=NOH, -CH=NNHCONH$_2$ or -NR^{5}R^6, wherein R^5 and R^6 independently from each other represent hydrogen or lower alkyl or together with the nitrogen atom, they are attached to, form a 5- or 6-membered, saturated or unsaturated heterocyclic ring optionally containing one or more further nitrogen, sulfur and/or oxygen atom(s); R^2 is nitro or amino; R^3 stands for hydrogen, lower alkanoyl or CO-NR^{7}R^8, wherein R^7 and R^8 independently from each other stand for hydrogen, lower alkoxy, lower alkyl or lower cycloalkyl or together with the nitrogen atom, they are attached to, form a 5- or 6-membered, saturated or unsaturated heterocyclic ring optionally containing one or more further nitrogen, sulfur and/or oxygen atom(s); R^4 is hydrogen or lower alkyl; the dotted lines have the following meaning: if R^3 and R^4 are not present, the bond between positions C^8 and C^9 is a single bond and the bond between positions C^8 and N^7 is a double bond; if R^3 and R^4 are present, the bonds between positions C^8 and C^9 and between position C^8 and N^7 are single bonds; and if R^3 is present and R^4 is missing, the bond between positions C^8 and C^9 is a double bond and the bond between positions C^8 and N^7 is a single bond) and salts thereof. The invention compounds have neuroprotective effect.

WO 01/04122 A2

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

New 2,3-benzodiazepine derivatives

TECHNICAL BACKGROUND

The invention relates to new 2,3-benzodiazepine derivatives, a process for the preparation thereof and pharmaceutical compositions containing the same. More particularly the invention is concerned with 1,3-dioxolo[4,5-h]-[2,3]-benzodiazepines bearing a 4-amino- or -nitro-3-methyl--phenyl-substituent in position 5, a process for the preparation thereof and pharmaceutical compositions containing the same.

STATE OF THE ART

In prior art several biologically active 2,3--benzodiazepine derivatives are described [e.g. HU 155 572, HU 179 018, HU 191 698, HU 191 702, HU 195 788 and HU 206 719]. Said known compounds possess anxiolytic, antidepressant, spasmolytic, muscle relaxant and neuroprotective properties.

Glutamic acid is the most important stimulating neurotransmitter of the central nervous system (stimulating amino acid). The receptors of the glutamic acid neurotransmitter can be divided into two groups, namely ionotropic receptors (attached to the ion channel) and metabotropic receptors. Ionotropic receptors play a role in almost every process of the function of the central nervous system, e.g. the function of learning, all types of memory, processes connected with acute and chronical

neurodegeneration and cell deterioration. Said receptors also play a role in pain sensation, motoric functions, urination reflex and cardiovascular homeostasis.

There are two types of ionotropic stimulating receptors, namely receptors of the NMDA and AMPA/cainate type. Receptors of the AMPA/cainate type are responsible in the first place for so-called quick synaptic functions, while NMDA receptors regulate slow synaptic proceedings disposed by quick synaptic processes. Thus receptors of the AMPA/cainate type may indirectly also influence the function of NMDA receptors. It follows from the aforesaid that numerous proceedings of the central nervous system and the whole organism can be regulated with the aid of antagonists of AMPA/cainate receptors.

There are two types of AMPA/cainate receptor antagonists, namely competitive and non-competitive antagonists. Due to the different character of inhibition, non-competitive antagonists are more favourable than competitive antagonists. The first representative of non-competitive antagonists is 1-(4-amino-phenyl)-4-methyl-7,8--methylenedioxy-5H-2,3-benzodiazepine which was synthetized about 15 years ago. Since the discovery of this compound several non-competitive AMPA/cainate antagonist 2,3-benzodiazepines have been prepared [S. D. Donevan et al.: J. Pharmacol. Exp. Ther., 271, 25-29 (1994); E. S. Vizi et al., CNS Drug Reviews, 2, 91-126 (1996)].

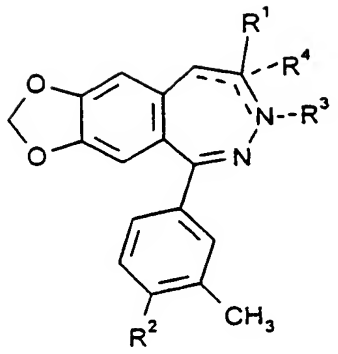
The therapeutical use of 2,3-benzodiazepines which exhibit a non-competitive antagonist effect on the AMPA/cainate receptor is manifold. The 2,3-benzodiazepines synthetized by research chemists of our company can be used as neuroprotective agents in case of symptoms accompanied by all types of acute and chronical neurodegeneration (e.g. Parkinson disease, Alzheimer disease, amyotropic lateral sclerosis, stroke, acute head injuries etc.). In addition to the above applications 2,3--benzodiazepines having AMPA/cainate antagonistic effect can also be used for the treatment of further symptoms, such as epilepsy, as spasmolytics, analgesics, antiemetic agents, against schizophreny, migraine, urination problems, as anxiolytics, against drug addiction, to alleviate the symptoms of Parkinsonism etc. [I. Tarnawa and E. S. Vizi, Restorative Neurol. Neurosci. 13, 41-57, (1998)].

DESCRIPTION OF THE INVENTION

It is the object of the present invention to provide new 2,3-benzodiazepine derivatives having favourable biological properties.

The above object is solved by the present invention.

According to the present invention there are provided new compounds of the general Formula



I

(wherein

R^1 stands for methyl, formyl, carboxy, cyano, -CH=NOH, $-CH=NNHCONH_2$ or $-NR^5R^6$, wherein

R^5 and R^6 independently from each other represent hydrogen or lower alkyl or together with the nitrogen atom, they are attached to, form a 5- or 6-membered, saturated or unsaturated heterocyclic ring optionally containing one or more further nitrogen, sulfur and/or oxygen atom(s);

R^2 is nitro or amino;

R^3 stands for hydrogen, lower alkanoyl or $CO-NR^7R^8$, wherein

R^7 and R^8 independently from each other stand for hydrogen, lower alkoxy, lower alkyl or lower cycloalkyl or together with the nitrogen atom, they are attached to, form a 5- or 6--membered, saturated or unsaturated heterocyclic ring optionally containing one or

more further nitrogen, sulfur and/or oxygen atom(s);

R^4 is hydrogen or lower alkyl;

the dotted lines have the following meaning:

if R^3 and R^4 are not present, the bond between positions C^8 and C^9 is a single bond and the bond between positions C^8 and N^7 is a double bond;

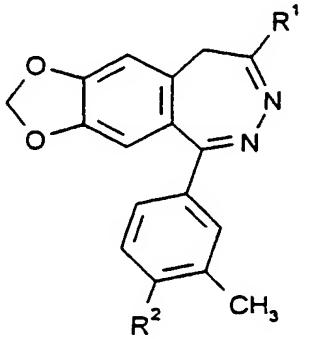
if R^3 and R^4 are present, the bonds between positions C^8 and C^9 and between positions C^8 and N^7 are single bonds; and

if R^3 is present and R^4 is missing, the bond between positions C^8 and C^9 is a double bond and the bond between positions C^8 and N^7 is a single bond)

and pharmaceutically acceptable acid addition salts thereof.

The compounds of the general Formula I can be divided into three groups, depending on the double bonds between positions 7,8 and 8,9.

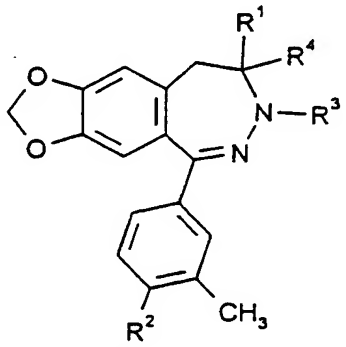
Compounds containing a single bond between positions C^8-C^9 and a double bond between positions C^8-N^7 and wherein R^3 and R^4 are not present, correspond to the general Formula



IA

(wherein R^1 and R^2 are as stated above).

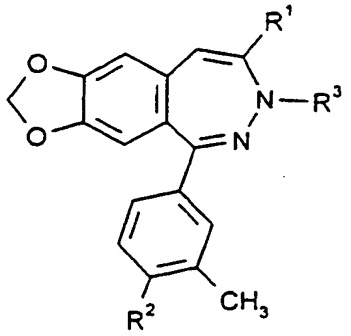
Compounds containing single bonds in positions C^8-C^9 and C^8-N^7 and wherein R^3 and R^4 are present, correspond to the general Formula



IB

(wherein R^1 and R^2 are as stated above).

Compounds containing a double bond between positions C^8 and C^9 and a single bond in positions C^8-N^7 and wherein R^3 is present and R^4 is missing, correspond to the general Formula



IC

(wherein R^1 and R^2 are as stated above).

DETAILED DESCRIPTION OF THE INVENTION

The terms used throughout the patent specification have the following definition.

The term "lower alkyl" relates to straight or branched saturated hydrocarbon groups containing 1-6, preferably 1-4 carbon atoms (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec. butyl etc.).

The term "lower alkoxy" relates to lower alkyl groups defined above attached through an oxygen atom (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy etc.).

The terms "lower cycloalkyl group" relates to cyclic hydrocarbon groups containing 3-6 carbon atoms (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl).

The term "5- or 6-membered saturated or unsaturated heterocyclic ring optionally containing one or more further nitrogen, sulfur and/or oxygen atom(s)" may be e.g. an imidazole, pyrazole, pyridazine, pyrazine, pyrrolidine, thiazole, thiazine, piperidine, piperazine or morpholine ring etc. Said heterocyclic ring may optionally bear one or more identical or different substituent(s) (e.g. lower alkyl, lower alkoxy, nitro, amino, hydroxy and/or halogen).

The term "pharmaceutically acceptable acid addition salt" relates to salts formed with pharmaceutically acceptable inorganic or organic acids. For salt formation e.g. the following acids can be used: hydrochloric acid, hydrogen bromide, sulfuric acid, phosphoric acid, formic acid, acetic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, succinic acid, citric acid, methanesulfonic acid, benzenesulfonic acid etc.

The compounds of the general Formula I contain a chiral carbon atom. The invention encompasses all stereoisomers of the compounds of the general Formula I and mixtures thereof, including the racemates.

In case of the presence of certain substituents, the compounds of the general Formula I can be present in the form of E- and Z-isomers (tautomery). The invention encompasses all E- and Z-isomers and tautomeric forms of the compounds of the general Formula I and mixtures thereof.

A preferred group of the invention compounds are derivatives of the general Formula I in which R^2 stands for amino.

Compounds of the general Formula IB in which R^2 stands for amino, possess particularly preferable properties.

A particularly preferred sub group of the compounds of the general Formula IB are derivatives in which R^1 stands for methyl or cyano; R^2 is amino; R^3 represents lower alkanoyl or $-CONR^7R^8$; R^7 is hydrogen; R^8 is lower alkyl, lower alkoxy or lower cycloalkyl and R^4 represents hydrogen or methyl.

A particularly preferred representative of the above compounds is the 7-acetyl-5-(4-amino-3-methyl-phenyl)-7,8--dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine.

The following compounds of the general Formula IB possess valuable properties as well:
5-(3-methyl-4-amino-phenyl)-7-propionyl-7,8-dihydro-8--methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;

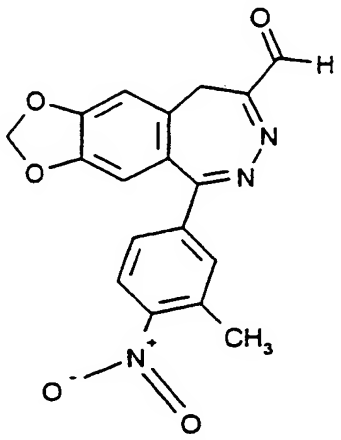
5-(4-amino-3-methyl-phenyl)-7-(N-cyclopropyl-carbamoyl)-7,8-
-dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-(N-methoxy-carbamoyl)-7,8-
-dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-(N-methyl-carbamoyl)-7,8-
-dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-acetyl-8-cyano-7,8-dihydro-8-
-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-8-cyano-7-propionyl-7,8-dihydro-
-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine.

A further preferable group of the compounds of the present invention are derivatives of the general Formula IC in which R^1 is methyl; R^2 stands for amino; R^3 is lower alkanoyl or -CO-NR^7R^8; R^7 is hydrogen and R^8 represents lower alkyl, lower alkoxy or lower cycloalkyl.

Preferred representatives of the compounds of the general Formula IC are the following derivatives:
7-acetyl-5-(4-amino-3-methyl-phenyl)-8-methyl-7H-1,3-
-dioxolo[4,5-h][2,3]benzodiazepine;
7-(N-methyl-carbamoyl)-5-(4-amino-3-methyl-phenyl)-8-
-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
7-(N-cyclopropyl-carbamoyl)-5-(4-amino-3-methyl-phenyl)-8-
-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine.

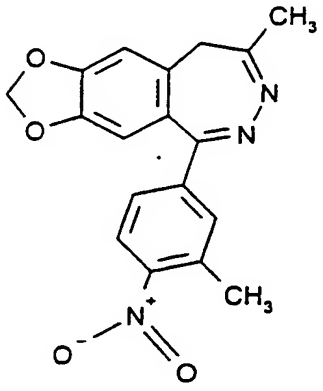
According to a further aspect of the present invention there is provided a process for the preparation of compounds of the general Formula I and pharmaceutically acceptable acid addition salts thereof which comprises

a) for the preparation of 8-formyl-5-(3-methyl-4-nitro--phenyl)-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine of the Formula



III

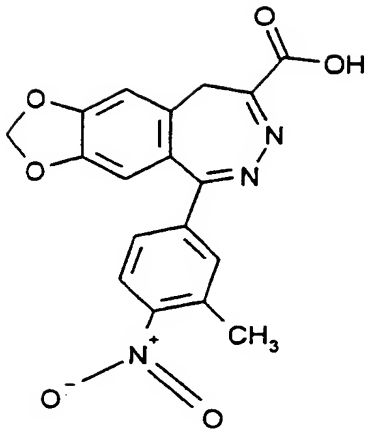
oxidizing 8-methyl-5-(4-nitro-3-methyl-phenyl)-9H-1,3--dioxolo[4,5-h][2,3]benzodiazepine of the Formula



II

or

b) for the preparation of 5-(3-methyl-4-nitro-phenyl)--9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-8-carboxylic acid of the Formula

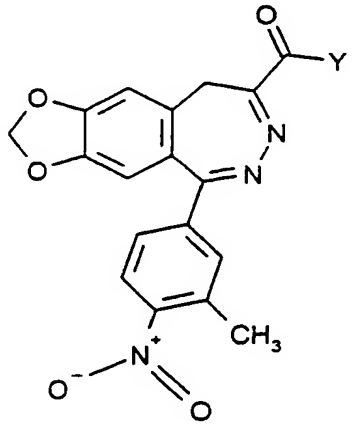


IV

oxidizing 8-formyl-5-(3-methyl-4-nitro-phenyl)-9H-1,3--dioxolo[4,5-h][2,3]benzodiazepine of the Formula III;

or

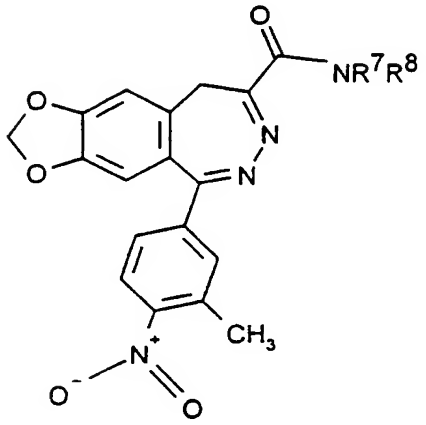
c) for the preparation of compounds of the general Formula



V

(wherein Y stands for a leaving group), reacting the compound of the Formula IV with a compound capable of introducing group Y; or

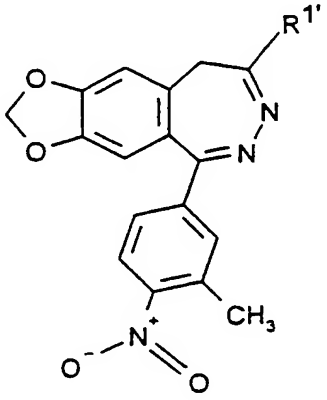
d) for the preparation of the compound of the general Formula



VI

(wherein R^7 and R^8 are as stated above), reacting the carboxylic acid of the Formula IV or a reactive derivative thereof of the Formula V with an amine of the general Formula HNR^7R^8; or

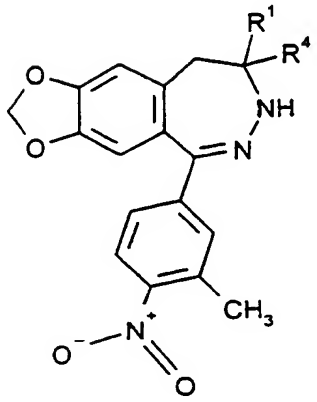
e) for the preparation of compounds of the general Formula



VII

(wherein $R^{1'}$ stands for cyano, -CH=NOH or $-CH=NNHCONH_2$), converting in the compound of the Formula III the formyl group into an $R^{1'}$ group; or

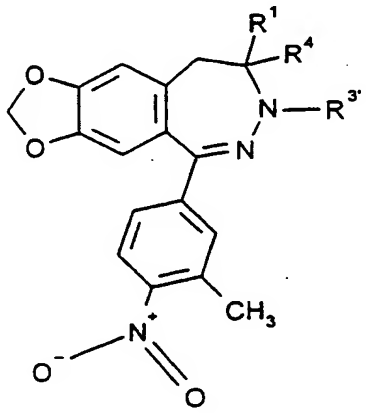
f) for the preparation of compounds of the general Formula



VIII

(wherein R^1 and R^4 are as stated above), saturating the C^8-N^7 double bond by addition or reduction; or

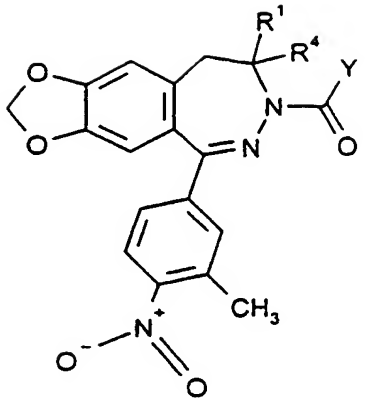
g) for the preparation of compounds of the general Formula



IX

(wherein $R^{3'}$ is lower alkanoyl), reacting a compound of the general Formula VIII with a compound capable of introducing a lower alkanoyl group; or

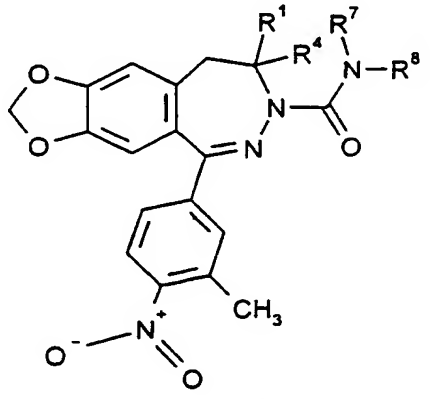
h) for the preparation of compounds of the general Formula



X

(wherein Y is a leaving group and R^1 and R^4 are as stated above), reacting a compound of the general Formula VIII with a compound capable of introducing the -COY group; or

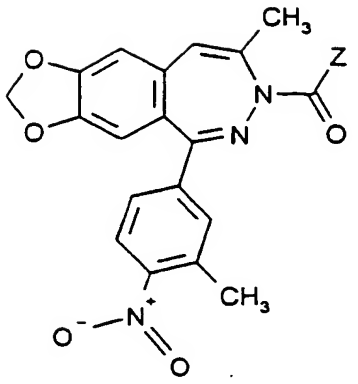
i) for the preparation of compounds of the general Formula



XI

(wherein R^1, R^4, R^7 and R^8 are as stated above), reacting a compound of the general Formula X or the corresponding free carboxylic acid with an amine of the general Formula HNR^7R^8; or

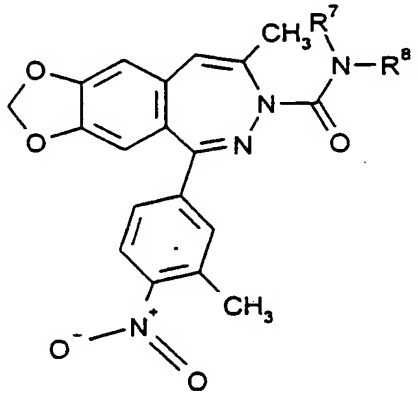
j) for the preparation of compounds of the general Formula



XII

(wherein Z stands for a leaving group), reacting the compound of the Formula II with a compound capable of introducing the -COZ group; or

k) for the preparation of compounds of the general Formula



XIII

(wherein R^7 and R^8 are as stated above), reacting a compound of the general Formula XII with an amine of the general Formula HNR^7R^8; or

l) for the preparation of compounds of the general Formula I, wherein R^2 stands for amino, reducing the corresponding compound of the general Formula I, wherein R^2 is nitro;

and, if desired, converting a compound of the general Formula I into a pharmaceutically acceptable acid addition salt thereof or setting free a compound of the general Formula I from a salt.

According to process a) in the compound of the Formula II the methyl group is oxidized into a formyl group to yield a compound of the Formula III. Oxidation may be carried out by methods known per se [Houben-Weyl: Methoden der organischen Chemie, Aldehyde, Band E3, Georg Thieme Verlag, Stuttgart, (1983)]. As oxidizing agent preferably selen(IV)oxide may be used. The compound of the Formula II can be prepared in an analogous manner to HU 191,702.

According to process b) the formyl compound of the general Formula III is oxidized into the carboxylic acid of the Formula IV. Oxidation may be carried out by methods known per se [Houben-Weyl: Methoden der organischen Chemie, Carbonsäure und Carbonsäure-Derivate, Band E5, Georg Thieme Verlag, Stuttgart, (1985); Saul Patai: The chemistry of acid derivatives, John Wiley and Sons, New York]. The reaction may be performed preferably with the aid of silver(I)nitrate in alkaline medium.

According to process c) the compounds of the general Formula V are prepared by reacting the carboxylic acid of the Formula IV with an agent capable of introducing the group Y. Said group Y is a suitable leaving group, e.g. halogen (e.g. chlorine or bromine), sulfonyloxy (e.g. alkyl- or aryl-sulfonyloxy, such as methylsulfonyloxy, p-bromo-

benzenesulfonyloxy, p-tolyl-sulfonyloxy or benzenesulfonyloxy etc.) or an imidazolyl group. Y represents particularly preferably an imidazolyl group. The process may be carried out by methods known per se [Houben-Weyl: Methoden der organischen Chemie, Carbonsäure und Carbonsäure-Derivate, Band E5, Georg Thieme Verlag, Stuttgart, (1985)]. The imidazolyl group may be introduced by reacting the compound of the Formula IV with 1,1'-carbonyl-diimidazole in a solvent as medium.

According to process d) the amino compounds of the general Formula VI are prepared by reacting the carboxylic acid of the Formula IV or a reactive derivative of the general Formula V thereof with an amine of the general Formula HNR^7R^8. The reaction may be carried out by methods known per se [Houben-Weyl: Methoden der organischen Chemie, Carbonsäure und Carbonsäure-Derivate, Band E5, Georg Thieme Verlag, Stuttgart, (1985); Saul Patai: The chemistry of amide group, Interscience Publishers, 1970)]. It is preferred to use compounds of the general Formula V in which Y is imidazolyl.

According to process e) the compounds of the general Formula VII are prepared by converting in the compound of the Formula III the formyl group into an $R^{1'}$ group. The process may be carried out by methods known per se [Houben-Weyl: Methoden der organischen Chemie, Carbonsäure und Carbonsäure-Derivate, Band E5, Georg Thieme Verlag, Stuttgart, (1985); Houben-Weyl: Methoden

der organischen Chemie, Organische Stickstoff-Verbindungen mit einer C,N-Doppelbindung, Teil 14, Georg Thieme Verlag, Stuttgart, (1990)]. Compounds of the general Formula VII, wherein $R^{1'}$ stands for a -CH=NOH group, may be prepared by reacting the compound of the Formula III with hydroxyl amine or a salt thereof (e.g. hydrochloride). On treating the product thus obtained with a dehydrating agent a compound of the general Formula VII is formed in which $R^{1'}$ stands for cyano. As dehydrating agent preferably methanesulfonyl chloride may be used. The compounds of the general Formula VII in which $R^{1'}$ is a -CH=NNHCONH$_2$ group may be prepared by reacting the compound of the Formula III with semicarbazide or a salt (e.g. hydrochloride) thereof.

According to process f) the compounds of the general Formula VIII are prepared by saturating the C^8-N^7 double bond by addition or reduction. According to an embodiment of said process hydrogen cyanide is added on the double bond of the compound of the Formula II. Thus compounds of the general Formula VIII are obtained in which R^1 is cyano and R^4 stands for methyl. According to a further embodiment of this process the C^8-N^7 double bond of a compound of the Formula II or VI is saturated to yield compounds of the general Formula VIII, wherein R^1 is methyl or a group of the Formula -CO-NR^{7}R^8. The above reactions may be carried out by known methods [Houben-Weyl: Methoden der organischen Chemie, Band IV, Reduktion, Georg Thieme Verlag, Stuttgart, (1989) or HU 186 760].

According to process g) the compounds of the general Formula IX are prepared by reacting a compound of the general Formula VIII with an agent capable of introducing a lower alkanoyl group. The process may be carried out by methods known per se. As acylating agent the corresponding acid chlorides, and anhydrides or chloro formiates may be used. The acylation reaction may be performed in the presence of an acid binding agent (e.g. pyridine). The reaction may be carried out at a temperature between -20°C and 150°C. The reaction may be performed in an organic solvent as medium, whereby an excess of the acylating agent may also act as solvent.

According to process h) the compounds of the general Formula X are prepared by reacting a compound of the general Formula VIII with an agent capable of introducing a -COY group. Y stands preferably for halogen, alkoxy, aryloxy, imidazolyl, pyrrolidinyl, piperidinyl or 1,2,4-triazolyl, particularly preferably for imidazolyl. The reaction may be carried out by using a hydrogen halide, halogeno formiate or 1,1'-carbonyl-diimidazole, depending on the definition of Y. The reaction may be performed at a temperature between -20°C and 150°C. The reaction may be carried out in the presence or absence of an acid binding agent (e.g. a pyridine derivative). According to a preferred embodiment of the process the imidazolyl group is introduced into the compound of the general Formula VIII with the aid of 1,1'-carbonyl-diimidazole.

According to process i) a compound of the general Formula XI is prepared by reacting a compound of the general Formula X with an amine of the general Formula HNR^7R^8. Amination may be carried out by methods known per se [Houben-Weyl: Amine, Bond XI, Georg Verlag, Stuttgart, (1957); S. Patai: The chemistry of amine group, Interscience Publishers, 1968)].

According to process j) the compounds of the general Formula XII are prepared by reacting a compound of the general Formula II with an agent capable of introducing the group -COZ. Symbol Z stands for a leaving group, preferably halogen, alkoxy or aryloxy. Acylation may be carried out preferably by using the corresponding acid halide, anhydride, 1,1'-carbonyl-diimidazole, hydrogen halide or halogeno formiate. The reaction may be carried out in the presence or absence of an acid binding agent. The reaction temperature is between -20°C and 150°C. In the course of the reaction the C^8-N^7 double bond present in the starting material of the Formula II is shifted into position C^8-C^9.

According to process k) the compounds of the general Formula XIII are prepared by reacting a compound of the general Formula XII with an amine of the general Formula NHR^7R^8. The reaction may be carried out by methods known per se [Houben-Weyl: Amine, Bond XI, Georg Verlag, Stuttgart, (1957); S. Patai: The chemistry of amine group, Interscience Publishers, 1968)].

According to process I) compounds of the general Formula I, wherein R^2 stands for amino, are prepared by reducing the corresponding compound of the general Formula I, wherein R^2 stands for nitro. Reduction is preferably carried out by using a nitro compound of the Formula II, VII, IX, XI, XII or XIII. The reaction can be carried out by methods known per se. Thus stannous(II)chloride, sodium dithionite or catalytic reduction may be used. In the latter case as catalyst Raney-nickel, palladium or platinum may be applied and hydrogen, hydrazine, hydrazine hydrate, formic acid, trialkyl ammonium formiate or an aikali formiate may serve as hydrogen source.

The compounds of the general Formula I can be converted into pharmaceutically acceptable acid addition salts or can be set free from their salts with a stronger base. These processes can be carried out by methods known per se.

Due to their non-competitive AMPA antagonistic activity the compounds of the general Formula I and pharmaceutically acceptable acid addition salts thereof exhibit among others a significant spasmolytic, muscle relaxant and neuroprotective effect and can be potentially used in case of any disease or symptom in which the inhibition of the stimulating amino acid receptors is preferred. The 2,3-benzodiazepines of the general Formula I may be used in all cases wherein antagonists of the AMPA/cainate non-competitive 2,3--benzodiazepine type are effective. Thus the compounds of the general Formula I can be used e.g. in the following indications: as neuroprotective agent in the treatment of

symptoms accompanied by all kinds of acute or chronical neurodegeneration, e.g. Parkinson disease, Alzheimer disease, amyotropic lateral sclerosis, stroke, acute head injuries. In addition the compounds of the general Formula I can also be used to improve various symptoms, e.g. epilepsy, as spasmolytics, analgesics, as anti-emetic agents, against schizophreny, migraine, urinating problems, as anxyolitic agents, against drug addiction and to alleviate the symptoms of Parkinsonism.

The 2,3-benzodiazepine ring of the compounds of the general Formula I bear a methyl group in ortho position related to the p-amino-group of the phenyl ring. The presence of said methyl group causes an increase of effect which manifests itself in a strengthening of the effect and/or a prolongation of the duration of effect. It has been surprisingly found that in the invention compounds bearing a methyl group in ortho position acetylation of the p-amino-group in inhibited. Since N-acetylation is an important metabolic step and furthermore the N-acetyl-2,3-benzodiazepines exhibit only a weak biological effect or are even inactive, due to the inhibited acetylation inactivation of the compounds takes place more slowly and consequently the biological effect increases.

The compounds of the general Formula I and salts thereof possess spasmolytic, muscle relaxant and neuroprotective effect and can be potentially used in case of any disease or symptom in which the inhibition of the stimulating amino acid receptors is preferred. The 2,3-

-benzodiazepines of the general Formula I may be used in all cases wherein antagonists of the AMPA/cainate non-competitive 2,3-benzodiazepine type are effective. Thus the compounds of the general Formula I can be used e.g. in the following indications: as neuroprotective agent in the treatment of symptoms accompanied by all kinds of acute or chronical neurodegeneration, e.g. Parkinson disease, Alzheimer disease, amyotropic lateral sclerosis, stroke, acute head injuries. In addition the compounds of the general Formula I can also be used to improve various symptoms, e.g. epilepsy, as spasmolytics, analgesics, as anti-emetic agents, against schizophreny, migraine, urinating problems, as anxyolitic agents, against drug addiction and to alleviate the symptoms of Parkinsonism.

According to a further aspect of the present invention there are provided pharmaceutical compositions containing as active ingredient a compound of the general Formula I or a pharmaceutically acceptable acid addition salt thereof.

The pharmaceutical compositions of the present invention can be administered orally (e.g. tablets, coated tablets, capsules, dragées, solutions, suspensions or emulsions), parenterally (e.g. intravenous, intramuscular or intraperitoneal injectable compositions), rectally (e.g. suppositories) or topically (e.g. ointments). The solid or liquid pharmaceutical compositions according to the invention can be prepared by methods of pharmaceutical industry known per se.

Oral solid pharmaceutical compositions may contain binders (e.g. gelatine, sorbitol, polyvinyl pyrrolidone etc.), carriers (e.g. lactose, glucose, starch, calcium phosphate), tabletting auxiliary agents (e.g. magnesium stearate, talc, polyethylene glycol, silicic acid etc.) and wetting agents (e.g. sodium lauryl sulfate).

Oral liquid compositions may be e.g. solutions, suspensions or emulsions and may contain suspending agent (gelatine, carboxymethyl cellulose etc.), emulsifiers (e.g. sorbitan monooleate etc.), solvents (e.g. water, oils, glycerol, propylene glycol, ethanol) and stabilizing agents (e.g. methyl--p-hydroxy-benzoate).

Parenteral pharmaceutical compositions may be generally sterile solutions of the active ingredient formed with water or isotonic saline.

Rectal compositions (e.g. suppositories) contain the active ingredient dispersed in a suppository base (e.g. cocoa butter).

The pharmaceutical compositions of the invention may be prepared by methods of pharmaceutical industry known per se. The compound of the general Formula I or a pharmaceutically acceptable acid addition salt thereof is admixed with solid or liquid pharmaceutical carriers and/or auxiliary agents and brought to galenic form. The pharmaceutical composition forms and their preparation are described e.g. at Remington's Pharmaceutical Sciences, Edition 18, Mack Publishing Co., Easton, USA, (1990).

The pharmaceutical compositions according to the present invention contain generally 0.1-95 % by weight of a compound of the general Formula I or an acid addition salt thereof. The daily dose of the compound of the general Formula I depends on various factors (e.g. efficiency of the active ingredient, age, body weight and general health of the patient, mode of administration, severeness of the disease to be treated etc.). The average daily dose is between 0.5 mg and 1000 mg for adults, preferably 20-200 mg of a compound of the general Formula I. Said amount may be administered in one or more dose(s). In case of urgency a single dose of 10-1000 mg may be administered.

According to a further feature of the invention there is provided the use of compounds of the general Formula I and pharmaceutically acceptable acid addition salts thereof for the preparation of pharmaceutical compositions having neuroprotective effect useful for the treatment of symptoms accompanied by all types of acute or chronical neurodegeneration (e.g. Parkinson disease, Alzheimer disease, amyotropic lateral sclerosis, stroke, acute head injuries, epilepsy), compositions having spasmolytic, analgesic and anti-emetic effect; compositions for the treatment of schizophreny, migraine, urination problems, against anxiety, drug addiction and to alleviate the symptoms of drug addiction and Parkinsonism.

According to a further aspect of the invention there is provided a method for the treatment of the above diseases

which comprises administering to the patient in need of such treatment a pharmaceutically efficient amount of a compound of the general Formula I or a pharmaceutically acceptable acid addition salt thereof.

The unexpected finding of this invention was that a methyl substitution in ortho position to the p-amino group on the aniline moiety of 2,3-benzodiazepines resulted in a profound decrease of N-acetylation. Due to inhibited acetylation some effects of our compounds are stronger and longer lasting than those of the parent compounds in animal experiments. Decreased rate of N-acetylation can be advantageous in the human therapy since human beings can be fast or slow acetylators. Plasma level of a compound subject to N-acetylation as the main metabolic pathway can be markedly different in the fast and slow acetylator phenotypes that makes difficult to determine the proper treatment dose of such a compound. Our unexpected finding decreases the probability of having such difficulties in the fast and slow acetylating phenotypes in the human therapy.

We use the *parent compound* name for the known 2,3--benzodiazepines without ortho-methyl substitution.

Effect of the ortho substitution on the rate of N--acetylation

Method

Liver slices of (WI) BR rats were incubated in oxigenized Krebs-Ringer solution at 37°C in the presence of 50 μM 2,3-benzodiazepines (Compound A-F). 0.5 ml aliquots

were obtained from the incubation mixture after 0, 30 and 60 min.

2,3-benzodiazepines were chosen as internal standards for the experiments according to the retention times of the compounds measured. Plasma proteins were precipitated with perchloric acid and 2,3-benzodiazepines were extracted with chloroform after alkalization. After evaporation to dryness the residue was dissolved in eluent.

Beckman System Gold HPLC was used with a C-18 reversed-phase column and an UV detector at 240 nm. Different eluents were used for the optimal separation of the compounds: Eluent ***A***: 50% 2 mM heptafluorobutyric acid, 35% methanol, 15 % acetonitrile. Eluent ***B***: 55% 2 mM heptafluorobutyric acid, 25% methanol, 20 % acetonitrile. Eluent ***C***: 50% 2 mM heptafluorobutyric acid, 40% methanol, 10 % acetonitrile.

The percentage of N-acetyl metabolite content of the samples at a certain time was calculated as follows: the peak area of the metabolite was divided with the sum of the peak areas of the compound and the metabolite.

Equation:

$$\text{N-ac. met. (\%)}_t = 100 \frac{\text{N-ac.met. PA}_t}{\text{N-ac.met. PA}_t + \text{Compound PA}_t}$$

$_t$: time (30 or 60 min)

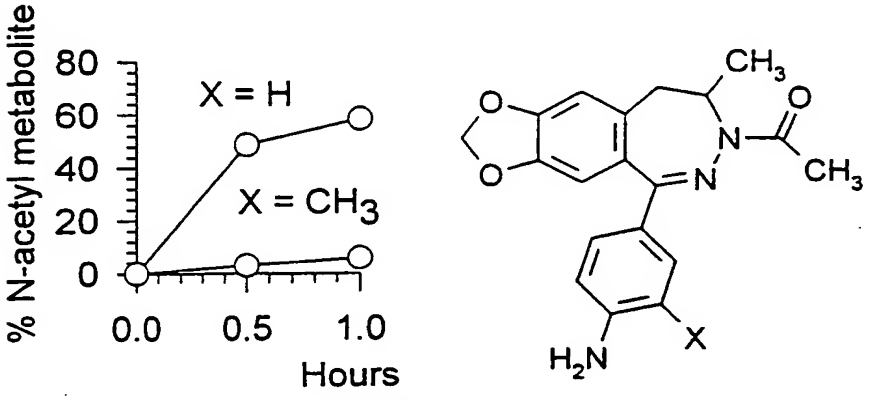
N-ac. met.: N-acetyl metabolite

PA: Peak Area

Results

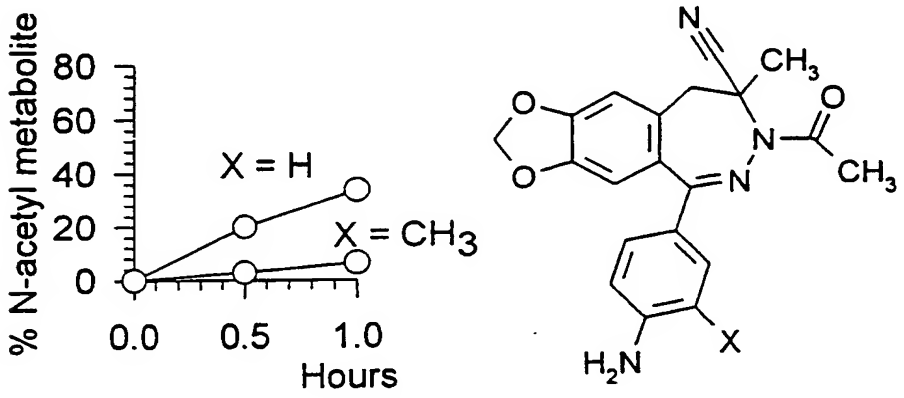
The next figures show that N-acetylation is always slower in the case of the o-methylated compounds than in the case of the parent ones, i. e. o-methylation inhibits the N--acetylation.

Compound A X = H X = CH_3



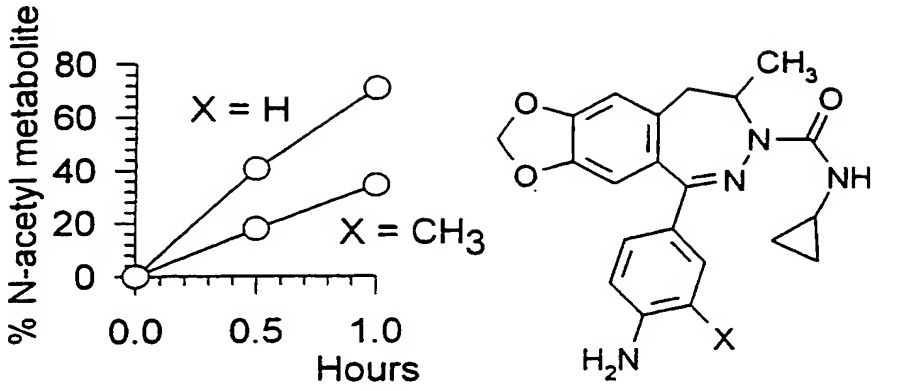
(Example 27)

Compound B X = H X = CH_3



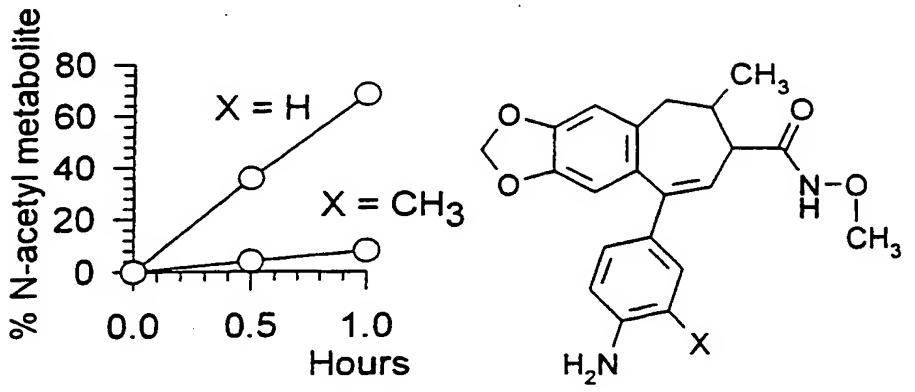
(Example 38)

Compound C X = H X = CH_3



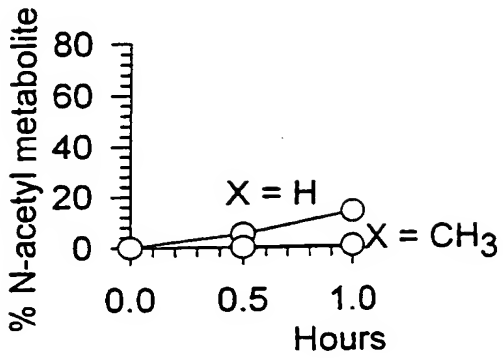
(Example 29)

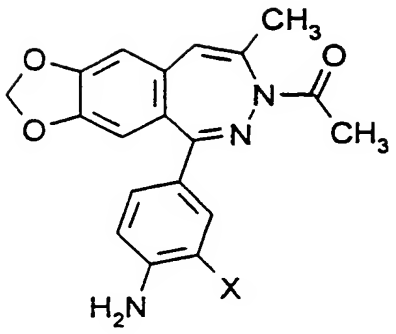
Compound D X = H X = CH_3



(Example 30)

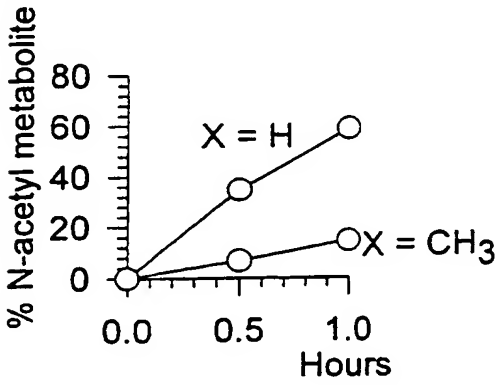
Compound E X = H X = CH_3

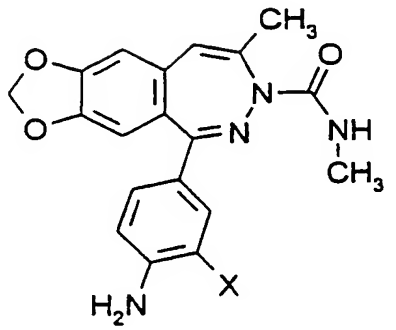




(Example 35)

Compound F X = H X = CH_3





(Example 36)

Neuroprotective effect in MgCl2-induced global cerebral ischemia in mice

Method

Male NMRI mice weighing 20-25 g were randomly allocated to treatment groups of 10 animals/group. The compounds were dissolved in 5 M hydrochloric acid solution and distilled water (5 %/95 % v/v) then the pH of the solution was adjusted to 3 using 1 M sodium hydroxide solution. The compounds were administered intraperitoneally in a volume of 10 ml/kg. Each compound was tested at four increasing dose levels and a separate group of animals was treated with the vehicle. Thirty min after treatment all mice received an intravenous bolus injection of saturated $MgCl_2$ solution (5 ml/kg) that caused an immediate cardiac arrest and complete cerebral ischemia. Increases in survival time (interval between the injection of $MgCl_2$ and the last observable gasp) were used as a measure of neuroprotective effect as described by Berga et al. [1]. Percentage changes in survival time were calculated in comparison to that measured in the vehicle treated group. PD_{50} (the dose that prolonged survival by 50 %) was calculated by linear regression analysis using percentage changes in survival time.

Results

The table shows the effects of compounds on survival time in mice in comparison to their parent compounds.

Test compound Example No.	X = H PD_{50}, mg/kg i.p.	X = CH_3 PD_{50}, mg/kg i.p.
Compound A Example 27	8.3	5.4
Compound B Example 38	18.7	11.2
Compound D Example 30	27.4	14.9

PD_{50} of all three o-substituted derivatives of the table was lower than that of their parent compounds. This means that o-methylation increased the neuroprotective effect of the compounds.

Reference

1. Berga, P., Beckett, P. R., Roberts, D. J., Llenas, J., Massingham, R.: Synergistic interactions between piracetam and dihydroergocristine in some animal models of cerebral hypoxia and ischaemia., Arzneim.-Forsch. 36, 1314-1320 (1986).

Duration of action in rats as assessed from the decrease in body core temperature

Method

At least one week prior to treatments six male Wistar rats were anaesthetised with pentobarbital-Na (60 mg/kg, i.p.; Nembutal, Phylaxia-Sanofi, Budapest). Using sterile surgical procedures TL11M2-C50-PXT or TA10TA-F40 type radiotelemetry transmitters (Data Sciences International, St. Paul, Minnesota, USA) permitting continuous monitoring of

core body temperature were implanted into the peritoneal cavity of the animals. After surgery the rats were treated with an antibiotic (1 ml/kg b.w. i.m. Tardomyocel, Bayer AG, Leverkusen, Germany). The animals were housed individually in type 2 plastic rat cages with free access to food and tap water. The compounds were dissolved in 5 M hydrochloric acid solution and distilled water (5 %/95 % v/v) then the pH of the solution was adjusted to 3 using 1 M sodium hydroxide solution. The compounds were administered intraperitoneally in a volume of 10 ml/kg.

Radio signals emitted by the transmitters were detected by RLA1000 type receivers placed under each animal's cage. Data were collected and saved by a Dataquest IV computerised data acquisition system. The computer was set to sample body temperature for 10 seconds in every second minute. Mean values for 30 min periods over the whole day were calculated running the "Sort Utility" of the Dataquest IV. System. The upper and lower limits of the evaluating routine were set to exclude biologically improbable values. Individual body temperature curves were averaged for the six animals.

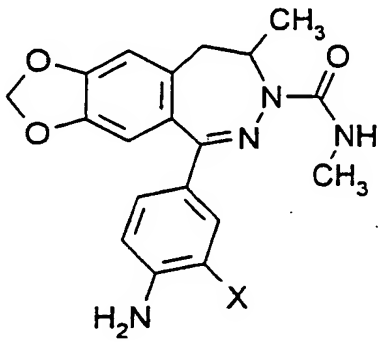
Peak effect (PE) was measured as the maximum decrease in body temperature in comparison to the last value prior to treatment. Using mean values, duration of action (D) was measured as the time interval from treatment to return of body temperature to the control level.

Results

The table shows the peak effect (PE) of different o-substituted derivatives on body temperature in rats in comparison to their parent compounds.

Test compound Example No.	X = H PE, Δ °C	X = CH_3 PE, Δ °C
Compound A Example 27	-1.26	-1.45
Compound B Example 38	-0.93	-1.34
Compound G Example 31	-1.12	-1.46

Compound G:



(Example 31)

The table shows the duration of action (D) of different o-substituted derivatives on body temperature in rats in comparison to their parent compounds.

Test compound Example No.	X = H D, hours	X = CH_3 D, hours
Compound A Example 27	5	> 20
Compound B Example 38	6	9
Compound G Example 31	5	20

The maximum decrease in body temperature was larger and the duration of action was longer for the different o--substituted derivatives in comparison to their parent compounds. This means that the o-methylation results in a stronger and longer lasting effect then its parent compound.

Further details of the present invention are to be found in the following Examples without limiting the scope of protection to said Examples.

Example 1

(±)-3-methyl-1-(3-methyl-4-nitro-phenyl)-1,3-dioxolo[4,5--g]isochromane

To a solution of 3.30 g (20.0 millimoles) of 3-methyl-4--nitro-benzaldehyde and 3.60 g (20.0 millimoles) of (±)-5-(2--hydroxy-1-propyl)-1,3-dioxolo[4,5-a]benzene in 40 ml of toluene 3.0 ml of concentrated hydrochloric acid are added. The reaction mixture is stirred at room temperature for a day, whereupon the mixture is diluted with 60 ml of toluene, washed with 40 ml of water, 20 ml of a concentrated sodium carbonate solution and 20 ml of a saturated sodium chloride solution, dried over magnesium sulfate and evaporated in vacuo. The crude product obtained is recrystallized from 80 ml of ethanol. Thus 4.59 g of the desired compound are obtained, yield 76 %, mp.: 122-123 °C.

$C_{18}H_{17}NO_5$ (327.34)

^1H NMR ($CDCl_3$) δ 7.96 (1H, d, J=8.8 Hz), 7.32 (2H, s), 6.60 (1H, s), 6.07 (1H, s), 5.87 (1H, d, J=1.2 Hz), 5.85 (1H, d, J=1.2 Hz), 5.66 (1H, s), 4.95 (1H, m), 2.75 (2H, m), 2.60 (3H, s), 1.38 (3H, d, J=6.0 Hz).

Example 2

5-(3-methyl-4-nitro-benzoyl)-6-(2-oxo-1-propyl)-1,3--dioxolo[4,5-a]benzene

3.28 g (10.0 millimoles) of (±)-3-methyl-1-(3-methyl-4--nitro-phenyl)-1,3-dioxolo[4,5-g]isochromane are dissolved in 60 ml of acetone, whereupon 10 ml of a Jones reagent containing 2.60 g (26.0 millimoles) of CrO_3 and 2.15 ml of

concentrated sulfuric acid are added dropwise under cooling with icecold water. The reaction mixture is stirred at room temperature for a day, whereupon the acetone is decanted and the residue is evaporated. The evaporation residue and the unsoluble part of the reaction mixture are taken up in a mixture of 75 ml of dichloro methane and 75 ml of water. The phases are separated and the aqueous layer is extracted twice with 50 ml of dichloro methane each. The united organic phases are washed with 50 ml of water, 50 ml of a saturated sodium chloride solution, dried over magnesium sulfate and evaporated in vacuo. The crude product obtained is crystallized from 50 ml of ethanol. Thus 2.15 g of the desired compound are obtained, yield 62 %, mp.: 146-148 °C.

$C_{18}H_{15}NO_6$ (341.32)

^{1}H NMR ($CDCl_3$) δ 7.97 (1H, d, J=8.3 Hz), 7.70 (1H, s), 7.66 (1H, d, J=8.4 Hz), 6.82 (1H, s), 6.74 (1H, s), 6.04 (2H, s), 3.97 (2H, s), 2.61 (3H, s), 2.22 (3H, s).

Example 3

3-methyl-1-(3-methyl-4-nitro-phenyl)-1,3-dioxolo[4,5--g]benzpyrilium-perchlorate

1.73 g (5.07 millimoles) of 4-(3-methyl-4-nitro--benzoyl)-5-(2-oxo-1-propyl)-1,3-dioxolo[4,5-a]-benzene are dissolved in 50 ml of ethyl acetate, whereupon 0.85 g (0.51 ml, 5.93 millimoles) of 70 % perchloric acid are added and the reaction mixture is stirred under boiling for an hour and thereafter cooled to 4 °C by cooling with ice-cold water. The precipitated product is filtered and washed with 10 ml of

cold ethyl acetate. Thus 2.08 g of the desired compound are obtained, yield 97 %, mp.: 262-266 °C.

$C_{18}H_{14}ClNO_9$ (423.77)

Example 4

8-methyl-5-(3-methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine

1.90 g (4.48 millimoles) of 3-methyl-1-(3-methyl-4-nitro--phenyl)-1,3-dioxolo[4,5-g]benzpyrilium-perchlorate are suspended in 35 ml of methanol, whereupon 1.31 g (1.30 ml, 26.23 millimoles) of 100 % hydrazine hydrate are added and the reaction mixture is stirred at room temperature for a day. The mixture is evaporated in vacuo and the residue is taken up in 50 ml of dichloro methane. The organic solution is washed three times with 20 ml of water each, drived over magnesium sulfate and evaporated in vacuo. The crude product obtained is recrystallized from 15 ml of ethanol. Thus 1.20 g of the desired compound are obtained, yield 79 %, mp.: 189-194 °C.

$C_{18}H_{15}N_3O_4$ (337.34)

^1H NMR ($CDCl_3$) δ 7.98 (1H, d, J=8.5 Hz), 7.74 (1H, s), 7.58 (1H, dd, J=8.5 and J=1.5 Hz), 6.78 (1H, s), 6.67 (1H, s), 6.07 (1H, s), 6.01 (1H, s), 3.30 (1H, d, J=12.3 Hz), 2.91 (1H, d, J=12.3 Hz), 2.63 (3H, s), 2.16 (3H, s).

Example 5

(±)-7,8-dihydro-8-methyl-5-(3-methyl-4-nitro-phenyl)-9H-1,3--dioxolo[4,5-h][2,3]benzodiazepine

1.69 g (10.0 millimoles) of 8-methyl-5-(3-methyl-4-nitro--phenyl)-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine are dissolved in a mixture of 75 ml of dichloro methane, 5 ml of methanol and 3 ml of glacial acetic acid. To the reaction mixture 0.38 g (10.0 millimoles) of sodium borohydride are added under cooling with ice-cold water in small portions. The reaction mixture is stirred at this temperature for an hour, then washed twice with 20 ml of water and 20 ml of saturated sodium chloride solution each, washed over magnesium sulfate and evaporated in vacuo. The crude product obtained is recrystallized from 50 ml of acetonitrile each. Thus 1.20 g of the desired compound are obtained, yield 71 %, mp.: 124--127 °C.

$C_{18}H_{17}N_3O_4$ (339.35)

^{1}H NMR ($CDCl_3$) δ 7.96 (1H, d, J=8.4 Hz), 7.52 (1H, s), 7.46 (1H, dd, J=8.4 and J=1.5 Hz), 6.74 (1H, s), 6.50 (1H, s), 5.98 (2H, s), 5.58 (1H, broad s), 4.09 (1H, m), 2.87 (1H, dd, J=13.9 and J=4.0 Hz), 2.62 (1H, dd, J=13.6 and J=6.6 Hz), 2.61 (3H, s), 1.27 (3H, d, J=6.2 Hz).

Example 6

(±)-7-acetyl-7,8-dihydro-8-methyl-5-(3-methyl-4-nitro-phenyl)--9H-1,3-dioxolo[4,5-h][2,3] benzodiazepine

1.70 g (5.0 millimoles) of (±)-7,8-dihydro-8-methyl-5-(3--methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5-

-h][2,3]benzodiazepine are stirred in 10 ml of acetic anhydride at room temperature for a day. The reaction mixture is poured into a mixture of 100 ml of water and 75 ml of dichloro methane, stirred for an hour and the pH is adjusted to 8 by adding sodium carbonate in portions. The layers are separated, the aqueous phase is extracted twice with 25 ml of dichloro methane each. The united organic phases are washed with 50 ml of saturated sodium chloride solution, dried over magnesium sulfate and evaporated. The crude product obtained is recrystallized from 15 ml of ethanol. Thus 1.65 g of the desired product are obtained, yield 87 %, mp.: 178-181 °C.

$C_{20}H_{19}N_3O_5$ (381.39)

^{1}H NMR ($CDCl_3$) δ 8.04 (1H, d, J=9.2 Hz), 7.50 (2H, m), 6.76 (1H, s), 6.49 (1H, s), 6.02 (2H, s), 5.38 (1H,m), 3.01 (1H, dd, J=13.6 and J=3.3 Hz), 2.76 (1H, dd, J=13.6 and J=8.4 Hz), 2.64 (3H, s), 2.29 (3H, s), 1.08 (3H, d, J=6.6 Hz).

Example 7

(±)-7,8-dihydro-8-methyl-5-(3-methyl-4-nitro-phenyl)-7--propionyl-9H-1,3-dioxolo[4,5-h][2,3] benzodiazepine

1.70 g (5.0 millimoles) of (±)-7,8-dihydro-8-methyl-5-(3--methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine are stirred in 10 ml of propionic anhydride at room temperature for a day. The reaction mixture is poured into a mixture of 100 ml of water and 75 ml of dichloro methane, stirred for an hour and the pH is adjusted to 8 by adding sodium carbonate in portions. The phases are

separated, the aqueous layer is extracted twice with 25 ml of dichloro methane each. The united organic layers are washed with 50 ml of a saturated sodium chloride solution, dried over magnesium sulfate and evaporated. The crude product obtained is recrystallized from 35 ml of diethyl ether. Thus 1.40 g of the desired product are obtained, yield 71 %, mp.: 172-175 °C.

$C_{21}H_{21}N_3O_5$ (395.42)

^1H NMR ($CDCl_3$) δ 8.00 (1H, d, J=9.6 Hz), 7.54 (2H, m), 6.77 (1H, s), 6.49 (1H, s), 6.01 (2H, s), 5.37 (1H,m), 2.98 (1H, dd, J=14.5 and J=3.4 Hz), 2.76 (1H, dd, J=14.6 and J=8.7 Hz), 2.66 (2H, m), 2.64 (3H, s), 1.14 (3H, t, J=7.4 Hz), 1.09 (3H, d, J=6.5 Hz).

Example 8

(±)-7,8-dihydro-8-methyl-5-(3-methyl-4-nitro-phenyl)-9H-1,3--dioxolo[4,5-h][2,3]benzodiazepine-7-carboxylic acid--imidazolide

A mixture of 3.37 g (10.0 millimoles) of (±)-7,8-dihydro--8-methyl-5-(3-methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine, 1.95 g (12.0 millimoles) of 1,1'--carbonyl-diimidazole and 75 ml of anhydrous tetrahydrofurane is stirred under boiling for 20 hours. The reaction mixture is cooled with icecold water. The precipitated product is filtered and washed with 50 ml of diethyl ether. Thus 3.55 g of the desired product are obtained, yield 82 %, mp.: 223-226 °C.

$C_{22}H_{19}N_5O_5$ (433.43)

^{1}H NMR ($(CD_3)_2SO$) δ 8.06 (1H, d, J=8.5 Hz), 7.96 (1H, s), 7.57 (1H, s), 7.54 (1H, dd, J=8.5 Hz and J=1.5 Hz), 7.38 (1H, s), 7.04 (1H, s), 7.13 (1H, s), 6.87 (1H, s), 6.13 (1H, d, J=0.8 Hz), 6.10 (1H, d, J=0.9 Hz), 5.08 (1H, m), 3.30 (3H, s), 3.05 (1H, dd, J=14.3 and J=5.0 Hz), 2.73 (1H, dd, J= 14.2 and 10.2 Hz), 1.30 (3H, d, J=6.2 Hz).

Example 9

(±)-7-(N-cyclopropyl-carbamoyl)-7,8-dihydro-8-methyl-5-(3--methyl-4-nitro-phenyl)-9H-1,3-dioxolo [4,5-h]-[2,3]benzodiazepine

4.33 g (10.0 millimoles) of (±)-7,8-dihydro-8-methyl-5--(3-methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine-7-carboxylic acid-imidazolide are heated to boiling in 30 ml of cyclopropyl amine for 6 hours, whereupon the amine is distilled off in vacuo. The residue is taken up in 75 ml of dichloro methane, washed three times with 30 ml of water each, dried over magnesium sulfate and evaporated in vacuo. The crude product obtained is recrystallized from 40 ml of ethanol and washed with 10 ml of diethyl ether. Thus 3.00 g of the desired compound are obtained, yield 71 %, mp.: 171-175 °C.

$C_{22}H_{22}N_4O_5$ (422.44)

^{1}H NMR ($CDCl_3$) δ 8.01 (1H, d, J=8.4 Hz), 7.41 (2H, m), 6.71 (2H, s), 6.45 (1H, s), 6.00 (1H, s), 5.99 (1H, s), 5.48 (1H, m), 3.10 (1H, m), 2.85 (1H, dd, J= 14.5 and 7.2 Hz), 2.68 (1H, m), 2.63 (3H, s), 0.95 (3H, d, J=6.6 Hz), 0.77 (2H, m), 0.54 (2H, m).

Example 10

(±)-7,8-dihydro-8-methyl-5-(3-methyl-4-nitro-phenyl)-7-(N--methoxy-carbamoyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine

2.03 g (25.0 millimoles) of methoxy-amine hydrochloride and 3.45 g (25.0 millimoles) of potassium carbonate are stirred in 75 ml of anhydrous dimethyl formamide for half an hour whereupon 2.17 g (5.0 millimoles) of (±)-7,8-dihydro--8-methyl-5-(3-methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine-7-carboxylic acid-imidazolide are added. The reaction mixture is stirred for 16 hours, whereupon the solvent is evaporated at a pressure of 55 Pa. The residue is suspended in 100 ml of water, stirred for half an hour, washed with 50 ml of water and dried. The crude product is recrystallized from 30 ml of acetonitrile and washed with 10 ml of diethyl ether. Thus 1.59 g of the desired compound are obtained, yield 77 %, mp.: 192-195 °C.

$C_{20}H_{20}N_4O_6$ (412.41)

^{1}H NMR ($CDCl_3$) δ 8.90 (1H, s), 8.00 (1H, d, J=9.2 Hz), 7.41 (2H, m), 6.73 (1H, s), 6.45 (1H, s), 6.01 (1H, m), 5.35 (1H, m), 3.81 (3H, s), 3.12 (1H, dd, J=14.7 and J=2.2 Hz), 2.85 (1H, dd, J= 14.7 and J=6.6 Hz), 2.64 (3H, s), 1.00 (3H, d, J=6.6 Hz).

Example 11

(±)-7,8-dihydro-8-methyl-7-(N-methyl-carbamoyl)-5-(3-methyl--4-nitro-phenyl)-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

A mixture of 2.17 g (5.0 millimoles) of (±)-7,8-dihydro-8--methyl-5-(3-methyl-4-nitro-phenyl)-9H-1,3dioxolo[4,5-

-h][2,3]benzodiazepine-7-carboxylic acid-imidazolide, 75 ml of dichloro methane and 15 ml of a 33 % ethanolic methyl amine solution is stirred for 3 hours. The reaction mixture is evaporated in vacuo and the residue is suspended in 75 ml of water. The crude product is filtered off, washed with 25 ml of water, dried and recrystallized from 25 ml of ethanol. Thus 1.68 g of the desired compound are obtained, yield 85 %, mp.: 221-229 °C.

$C_{20}H_{20}N_4O_5$ (396.41)

^1H NMR ($CDCl_3$) δ 8.00 (1H, d, J=9.2 Hz), 7.40 (2H, m), 6.72 (1H, s), 6.53 (1H, m), 6.46 (1H, s), 6.01 (1H, s), 6.00 (1H, s), 5.463 (1H, m), 3.11 (1H, m), 2.89 (4H, m), 2.64 (3H, s), 0.95 (3H, d, J=6.6 Hz).

Example 12

8-formyl-5-(3-methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine

A mixture of 3.37 g (10.0 millimoles) of 8-methyl-5-(4--nitro-3-methyl-phenyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine, 1.66 g (10.5 millimoles) of selen(IV)oxide and 100 ml of dioxane is stirred on an oil-bath at 80 °C for 3 hours. The solution is filtered on a hot coal-bed washed with 50 ml of hot dioxane and evaporated in vacuo. The crude product obtained is treated with 20 ml of acetonitrile. Thus 2.42 g of the desired compound are obtained, yield 69 %, mp.: 188-191 °C.

$C_{18}H_{13}N_3O_5$ (337.29)

^{1}H NMR ($CDCl_3$) δ 9.54 (1H, s), 8.02 (1H, d, J=8.4 Hz), 7.79 (1H, s), 7.65 (1H, dd, J=8.4 Hz and J=1.8 Hz), 6.82 (1H, s), 6.61 (1H, s), 6.15 (1H, d, J=07 Hz), 6.03 (1H, d, J=1.1 Hz), 4.11 (1H, d, J=12.8 Hz), 2.62 (1H, d, J=12.1 Hz), 2.66 (3H, s)

Example 13

5-(3-methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine-8-carboxylic acid

To a solution of 3.40 g (20.0 millimoles) of silver(I)nitrate and 25 ml of water a solution of 1.60 g (4.0 millimoles) of sodium hydroxide and 25 ml of water is added. The mixture is stirred for 10 minutes, diluted with 50 ml of tetrahydrofurane and 3.51 g (10.0 millimoles) of 8--formyl-5-(3-methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine are added under cooling with icecold water. The reaction mixture is stirred at room temperature for 5 hours, filtered on a coal-bed and washed with cold water. The pH of the solution is adjusted to 2 with 6 N hydrochloric acid. After cooling the precipitated product is filtered and washed with 10 ml of cold water. Thus 2.61 g of the desired compound are obtained, yield 71 %, mp.: 185-186 °C.

$C_{18}H_{13}N_3O_6$ (367.32)

^{1}H NMR ($(CD_3)_2SO$) δ 13.40 (1H, broad s), 8.08 (1H, d, J=8.8 Hz), 7.74 (1H, s), 7.63 (1H, dd, J=8.3 Hz and J=1.5 Hz), 7.05 (1H, s), 6.83 (1H, s), 6.17 (1H, s), 6.10 (1H, s), 4.08 (1H, d, J=12.7 Hz), 2.75 (1H, d, J=12.7 Hz), 2.57 (3H, s).

Example 14

5-(3-methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5-h] -[2,3]benzodiazepine-8-carboxylic acid-imidazolide

3.67 g (10.0 millimoles) of 5-(3-methyl-4-nitro-phenyl)--9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-8-carboxylic acid are suspended in 75 ml of anhydrous dimethyl-formamide and 1.95 g (12.0 millimoles) of 1,1'-carbonyl-diimidazole are added in one portion. The reaction mixture is stirred at room temperature for 5 hours and cooled with icecold water. The precipitated product is filtered and washed with 50 ml of diethyl ether. Thus 3.21 g of the desired compound are obtained, yield 77 %, mp.: 132-136 °C.

$C_{21}H_{15}N_5O_5$ (417.38)

^{1}H NMR ($(CD_3)_2SO$) δ 8.53 (1H, s), 8.08 (1H, d, J=9.2 Hz), 7.81 (1H, s), 7.80 (1H, s), 7.66 (1H, d, J=8.3 Hz), 7.16 (1H, s), 7.10 (1H, s), 6.84 (1H, s), 6.18 (1H, s), 6.11 (1H, s), 4.17 (1H, d, J=13.6 Hz), 2.83 (1H, d, J=13.4 Hz), 2.58 (3H, s).

Example 15

5-(3-methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine-8-carboxylic acid-amide

4.17 g (10.0 millimoles) of 5-(3-methyl-4-nitro-phenyl)--9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-8-carboxylic acid--imidazolide are suspended in a mixture of 85 ml dichloro methane and 15 ml of a 15 % aqueous methanolic ammonia solution. The reaction mixture is sealed and stirred at room temperature for 6 hours. The mixture is cooled with icecold water. The precipitated product is filtered and washed with

20 ml of diethyl ether. Thus 3.11 g of the desired compound are obtained, yield 85 %, mp.: 266-268 °C.

$C_{18}H_{14}N_4O_5$ (366.34)

^1H NMR ($(CD_3)_2SO$) δ 8.08 (1H, d, J=8.4 Hz), 7.82 (1H, broad s), 7.73 (1H, broad s), 7.61 (2H, m), 7.01 (1H, s), 6.80 (1H, s), 6.16 (1H, s), 6.09 (1H, s), 4.23 (1H, d, J=12.5 Hz), 3.37 (3H, s), 2.64 (1H, d, J=12.5 Hz).

Example 16

(±)-7,8-dihydro-5-(3-methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine-8-carboxylic acid-amide

1.76 g (5.0 millimoles) of 5-(3-methyl-4-nitro-phenyl)--9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-8-carboxylic acid--amide are suspended in a mixture of 75 ml ethanol and 75 ml of dichloro methane, whereupon 0.19 g (5.0 millimoles) of sodium-[tetrahydrido-borate(IV)] are added in one portion and a solution of 0.55 g (5.0 millimoles) of calcium chloride in 25 ml of ethanol is added dropwise. The reaction mixture is stirred at room temperature for 25 hours and evaporated in vacuo. The residue is heated to boiling in 100 ml of water for half an hour and filtered hot. The crude product obtained is heated to boiling in 50 ml of acetonitrile for half an hour, cooled with icecold water, filtered and washed with 20 ml of diethyl ether. Thus 1.27 g of the desired compound are obtained, yield 69 %, mp.: 246-249 °C.

$C_{18}H_{16}N_4O_5$ (368.35)

^1H NMR ($(CD_3)_2SO$) δ 7.98 (1H, d, J=8.8 Hz), 7.72 (1H, d, J=5.1 Hz), 7.49 (1H, broad s), 7.41 (1H, d, J=8.1 Hz), 7.21

(2H, broad s), 6.82 (1H, s), 6.47 (1H, s), 6.03 (2H, s), 4.30 (1H, m), 3.35 (3H, s), 2.99 (2H, m).

Example 17

(±)-7-acetyl-7,8-dihydro-5-(3-methyl-4-nitro-phenyl)--9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-8-carboxylic acid--amide

3.68 g (10.0 millimoles) of (±)-7,8-dihydro-5-(3-methyl--4-nitro-phenyl)-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-8--carboxylic acid-amide are suspended in 30 ml of acetic anhydride and stirred at room temperature for 48 hours. The reaction mixture is cooled with icecold water, the precipitated product is filtered and washed with 20 ml of diethyl ether. Thus 3.32 g of the desired compound are obtained, yield 81 %, mp.: 157-161 °C.

$C_{20}H_{18}N_4O_6$ (410.39)

^1H NMR ($(CD_3)_2SO$) δ 8.05 (1H, d, J=8.1 Hz), 7.56 (2H, m), 7.27 (1H, broad s), 6.97 (1H, broad s), 6.87 (1H, s), 6.49 (1H, s), 6.07 (2H, s), 5.45 (1H, m), 3.18 (2H, m), 2.32 (3H, s), 2.22 (3H, s).

Example 18

8-cyano-5-(3-methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine

A mixture of 3.51 g (10.0 millimoles) of 8-formyl-5-(3--methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine, 0.83 g (12.0 millimoles) of hydroxyl--amine hydrochloride and 1.09 g (13.0 millimoles) of anhydrous sodium acetate and 100 ml of ethanol is stirred

under boiling for 10 hours, whereupon the reaction mixture is evaporated in vacuo. The residue is suspended in 150 ml of water, stirred at room temperature for half an hour, filtered and washed with 25 ml of water. The oxime thus obtained is dried, suspended in 100 ml of dichloro-methane, 2.42 g (3.34 ml, 24.0 millimoles) of triethyl amine are added and a solution of 1.32 g (0.93 ml, 12.0 millimoles of methane--sulfonyl chloride in 10 ml of dichloro methane is added dropwise under cooling with icecold water. The reaction mixture is stirred at room temperature for 4 hours, washed twice with 30 ml of water and 30 ml of a saturated sodium chloride solution each, drived over magnesium sulfate and evaporated in vacuo. The crude product thus obtained is recrystallized from 55 ml of acetonitrile and washed with 20 ml of diethyl ether. Thus 2.12 g of the desired compound are obtained, yield 61 %, mp.: 211-214 °C.

$C_{18}H_{12}N_4O_4$ (348.32)

^{1}H NMR ($(CD_3)_2SO$) δ 8.07 (1H, d, J=8.4 Hz), 7.75 (1H, d, J=1.8 Hz), 7.60 (1H, dd, J=8.4 Hz and J=1.8 Hz), 7.28 (1H, s), 6.88 (1H, s), 6.20 (1H, s), 6.15 (1H,s), 3.91 (1H, d, J=13.9 Hz), 3.18 (1H, d, J=13.8 Hz), 2.56 (3H, s).

Example 19

5-(3-methyl-4-nitro-phenyl)-8-(semicarbazono-methyl)-9H-1,3--dioxolo[4,5-h][2,3]benzodiazepine

A mixture of 3.51 g (10.0 millimoles) of 8-formyl-5-(3--methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine, 1.34 g (12.0 millimoles) of

semicarbazide hydrochloride, 1.01 g (12.0 millimoles) of anhydrous sodium acetate and 100 ml of anhydrous ethanol is stirred under boiling for 6 hours. The reaction mixture is evaporated in vacuo, the residue is suspended in 100 ml of water, stirred at room temperature for half an hour, filtered and washed with 25 ml of water. The crude product thus obtained is heated to boiling in 75 ml of acetone for half an hour, cooled with icecold water, the precipitated product is filtered and washed with 10 ml of cold acetone. Thus 3.34 g of the desired compound are obtained, yield 81 %, mp.: 260-264 °C.

$C_{19}H_{16}N_6O_5$ (408.38)

^{1}H NMR ($(CD_3)_2SO$) δ 10.63 (1H, s), 8.06 (1H, d, J=8.4 Hz), 7.42 (1H, d, J=1.4 Hz), 7.64 (1H, dd, J=8.4 Hz and J=1.7 Hz), 7.49 (1H, s), 7.26 (1H, s), 6.85 (2H, broad s), 6.77 (1H, s), 6.15 (1H, s), 6.08 (1H, s), 4.55 (1H, d, J=12.5 Hz), 2.63 (1H, d, J=12.4 Hz), 2.57 (3H, s).

Example 20

7-acetyl-8-methyl-5-(3-methyl-4-nitro-phenyl)-7H-1,3--dioxolo[4,5-h][2,3]benzodiazepine

A mixture of 3.37 g (10.0 millimoles) of 8-methyl-5-(3--methyl-4-nitro-phenyl)-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine and 25 ml acetyl chloride is stirred under boiling for 3 hours, whereupon the acid chloride is distilled off in vacuo. The residue is taken up in 100 ml of dichloro methane, washed with 50 ml of a saturated sodium carbonate solution and 50 ml of water. The organic phase is dried over magnesium sulfate and evaporated in vacuo. The

crude product obtained is recrystallized from 50 ml of acetonitrile. Thus 2.62 g of the desired compound are obtained, yield 69 %, mp.: 115-116 °C.

$C_{20}H_{17}N_3O_5$ (379.38)

^1H NMR ($CDCl_3$) δ 7.98 (1H, d, J=8.4 Hz), 7.52 (1H, d, J=1.8 Hz), 7.46 (1H, dd, J=8.4 Hz and J=1.8 Hz), 6.76 (1H, s), 6.52 (1H, s), 6.08 (1H, broad s), 6.03 (2H, broad s), 2.63 (3H, s), 2.28 (3H, s), 2.26 (3H, s).

Example 21

7-(N-methyl-carbamoyl)-8-methyl-5-(3-methyl-4-nitro-phenyl)--7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

3.37 g (10.0 millimoles) of 8-methyl-5-(3-methyl-4-nitro--phenyl)-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine are dissolved in 75 ml of anhydrous dioxane, whereupon 2.35 g (1.89 ml, 15.0 millimoles) of phenyl chloro formate are added, and the reaction mixture is stirred on an oil bath having a temperature of 80 °C for 3 hours. The solvent is distilled off in vacuo and to the residue 30 ml of a 33 % ethanolic methyl amine solution is added. The sealed flask is stirred at room temperature for an hour and evaporated. The residue is taken up in 100 ml of dichloro methane, washed twice with 50 ml of water each, dried over magnesium sulfate and evaporated in vacuo. The crude product obtained is crystallized from 75 ml of ethanol. Thus 2.44 g of the desired compound are obtained, yield 62 %, mp.: 246-248 °C.

$C_{20}H_{18}N_4O_5$ (394.39)

^{1}H NMR ($CDCl_3$) δ 7.98 (1H, d, J=8.1 Hz), 7.43 (2H, m), 6.69 (1H, s), 6.42 (1H, s), 6.15 (1H, s), 6.09 (1H, m), 6.01 (2H, s), 2.96 (3H, d, J=4.4 Hz), 2.62 (3H, s), 2.21 (3H, s).

Example 22

7-(N-cyclopropyl-carbamoyl)-8-methyl-5-(3-methyl-4-nitro--phenyl)-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

3.37 g (10.0 millimoles) of 8-methyl-5-(3-methyl-4-nitro--phenyl)-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine are dissolved in 75 ml of anhydrous dioxane, 2.35 g (1.89 millimoles) of phenyl chloro formate are added and the reaction mixture is stirred on an oil bath having a temperature of 80 °C for an hour and a half. The solvent is distilled off in vacuo, to the residue 15 ml of cyclopropyl amine are added and the mixture is heated to boiling for 2 days. The excess of the amine is distilled off in vacuo. The residue is taken up in 100 ml of dichloro methane, washed twice with 50 ml of water, dried over magnesium sulfate and evaporated in vacuo. The crude product obtained is recrystallized from 45 ml of acetonitrile. Thus 2.98 g of the desired compound are obtained, yield 71 %, mp.: 198-202 °C.

$C_{22}H_{20}N_4O_5$ (420.43)

^{1}H NMR ($CDCl_3$) δ 7.99 (1H, d, J=9.2 Hz), 7.42 (2H, m), 6.69 (1H, s), 6.41 (1H, s), 6.22 (1H, m), 6.15 (1H, s), 6.07 (2H, s), 2.77 (1H, m), 2.62 (3H, s), 2.21 (3H, s), 0.82 (2H, m), 0.62 (2H, m).

Example 23

(±)-8-cyano-7,8-dihydro-8-methyl-5-(3-methyl-4-nitro-phenyl)--9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

In a 100 ml bomb tube made of stainless steel 10.12 g (30.0 millimoles) of 8-methyl-5-(3-methyl-4-nitro-phenyl)-9H--1,3-dioxolo[4,5-h][2,3]benzodiazepine and 50 ml of glacial acetic acid are weighed in. To the suspension at 15-20 °C 5.90 g (90.6 millimoles) of potassium cyanide are added within 5 minutes under cooling with icecold water. The bomb tube is sealed. The reaction mixture is stirred at 70 °C for 24 hours, cooled, stirred with 350 ml of dichloro methane and 350 ml of water and the layers are separated. The aqueous phase is extracted with 150 ml of dichloro methane, the organic phases are washed with 50 ml of water, dried over magnesium sulfate and evaporated. The residue is crystallized from 100 ml of ether, filtered and washed with ether. Thus 10.40 g of the desired compound are obtained, yield 95 %, mp.: 148-151 °C.

$C_{19}H_{16}N_4O_4$ (364.35)

Example 24

(±)-7-acetyl-8-cyano-7,8-dihydro-8-methyl-5-(3-methyl-4-nitro--phenyl)-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

To 60 ml of acetyl chloride 9.11 g (25.0 millimoles) of (±)-8-cyano-7,8-dihydro-8-methyl-5-(3-methyl-4-nitro-phenyl)--9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine are added at 15 °C under stirring. The suspension formed turns into a solution within 5 minutes, but after a further period of 5 minutes a

suspension is re-formed. The reaction mixture is stirred at 25 °C for 6 days, whereupon it is evaporated in vacuo. To the residue 90 ml of water are added and the mixture is stirred under cooling with icecold water for half an hour. The precipitated crystals are filtered and washed with icecold water. The crude product is crystallized from 150 ml of acetonitrile. The crystals are filtered, washed with acetonitrile and ether and dried. Thus 6.84 g of the desired compound are obtained, yield 67 %, mp.: 253-255 °C.

$C_{21}H_{18}N_4O_5$ (406.40)

^{1}H NMR ($CDCl_3$) δ 8.01 (1H, d, J=9.0 Hz), 7.59 (2H, m), 6.99 (1H, s), 6.52 (1H, s), 6.10 (1H, d, J=1.3 Hz), 6.06 (1H, d, J=1.3 Hz), 3.08 (2H, s), 2.64 (3H, s), 2.28 (3H, s), 1.84 (3H, s).

Example 25

(±)-8-cyano-7,8-dihydro-8-methyl-5-(3-methyl-4-nitro-phenyl)--7-propionyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

To 55 ml of propionyl chloride 7.06 g (19.4 millimoles) of (±)-8-cyano-7,8-dihydro-8-methyl-5-(3-methyl-4-nitro--phenyl)-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine are added at 15 °C. The reaction mixture is stirred at 25 °C for 8 days and evaporated in vacuo. To the residue 200 ml of water are added. The mixture is stirred under cooling with icecold water for an hour. The precipitated crystals are filtered and washed with icecold water. The crude product obtained is recrystallized from 100 ml of acetonitrile. The crystals are filtered, washed with acetonitrile and ether and dried. Thus

6.30 g of the desired compound are obtained, yield 77 %, mp.: 191-193 °C.

$C_{22}H_{20}N_4O_5$ (420.41)

Examples 26-39

General methods for the reduction of the nitro group of compounds prepared according to Examples 1-25

Method A

5.0 millimoles of the nitro compound are dissolved in a mixture of 100 ml of dichloro methane and 50 ml of methanol. The solution is hydrogenated in the presence of 0.10 g of a 10 % palladium charcoal catalyst at a pressure of $5.065 \cdot 10^5$ Pa. After hydrogenation the catalyst is filtered off, the filtrate is evaporated in vacuo and the crude product obtained is recrystallized.

Method B

3.45 g (25.0 millimoles) of potassium carbonate, 3.92 g (22.5 millimoles) of sodium dithionite and 0.14 g (0.25 millimoles) of N,N'-bis-octadecyl-4,4'-bipyridinium-dibromide are dissolved in 100 ml of water, whereupon the solution or suspension of 5.0 millimoles of the nitro compound used as starting material formed with 100 ml of ethyl acetate is added under nitrogen. The reaction mixture is stirred at room temperature for 2-3 days and the layers are separated. The aqueous phase is extracted four times with 50 ml of ethyl acetate each. The united organic layers are washed with 50 ml of a saturated sodium chloride solution, dried over magnesium sulfate, filtered through a charcoal-bed and

evaporated in vacuo. The crude product obtained is recrystallized.

Method C

6.8 millimoles of the nitro compound are suspended in a mixture of 130 ml of ethanol and 30 ml of water. To the suspension 1.5 g of a 10 % palladium-charcoal catalyst are added, whereupon within 10 minutes 19.0 g (383.0 millimoles) of 98 % hydrazine hydrate are added. The reaction mixture warms to 36°C and the starting material goes into solution. The reaction mixture is stirred at room temperature for two hours and a half, whereby the reaction mixture cools to 25°C and the product precipitates. The catalyst is filtered off and washed twice with 100 ml of ethanol and twice with 200 ml of chloroform each. The filtrate is evaporated in vacuo. To the crystalline residue 300 ml of water are added, the mixture is stirred for an hour. The crystals are filtered and washed with water. The crude product thus obtained is recrystallized.

The characteristic data of the compounds thus obtained are summarized in the following Table I.

Table I

No. of Example	Nomenclature of compound	Brutto formula	Cystallizing solvent, Mp.°C	Yield (%)
26	5-(4-amino-3-methyl-phenyl)-9H-7,8--dihydro-8-methyl-1,3-dioxolo[4,5--h][2,3]benzodiazepine	$C_{18}H_{17}N_3O_2$ (307.36)	dimethyl--formamide 262-264	64
Method: A	Elementary analysis C: calc.: 70.34 (%), found: 69.99 (%); H: calc.: 5.58 (%), found: 5.38 (%); N: calc.: 13.67 (%), found: 13.25 (%)			
	^{1}H NMR ($(CD_3)_2SO$) δ 7.20 (1H, d, J=1.4 Hz), 7.10 (1H, dd, J=8.2 Hz and J=2.0 Hz), 7.03 (1H, s), 6.69 (1H, s), 6.62 (1H, s), 6.11 (1H, d, J=0.7 Hz), 6.05 (1H, s), 5.24 (2H, broad s), 3.34 (1H, d, J=12.0 Hz), 2.69 (1H, d, J=12.0 Hz), 2.07 (3H, s), 2.01 (3H, s).			
27	(±)-7-acetyl-5-(4-amino-3-methyl-phenyl)--7,8-dihydro-8-methyl-9H-1,3--dioxolo[4,5-h][2,3]benzodiazepine	$C_{20}H_{21}N_3O_3$ (351.41)	acetonitrile 121-123	75
Method: A	Elementary analysis C: calc.: 68.36 (%), found: 67.51 (%); H: calc.: 6.02 (%), found: 5.81 (%); N: calc.: 11.96 (%), found: 12.16 (%)			
	^{1}H NMR ($CDCl_3$) δ 7.47 (1H, s), 7.31 (1H, d, J=8.4 Hz), 6.76 (1H, s), 6.66 (1H, d, J=8.4 Hz), 6.58 (1H, s), 5.99 (2H, m), 5.22 (1H, m), 4.08 (2H, broad s), 2.66 (2H, m), 2.19 (3H, s), 2.01 (3H, s), 1.31 (3H, d, J=6.2 Hz).			
28	(±)-5-(3-methyl-4-amino-phenyl)-7,8--dihydro-8-methyl-7-propionyl-9H-1,3--dioxolo[4,5-h]-[2,3]benzodiazepine	$C_{21}H_{23}N_3O_3$ (365.44)	acetonitrile 170-172	78
Method: A	Elementary analysis C: calc.: 69.02 (%), found: 69.00 (%); H: calc.: 6.34 (%), found: 6.28 (%); N: calc.: 11.50 (%), found: 11.23 (%)			
	^{1}H NMR ($CDCl_3$) δ 7.46 (1H, broad s), 7.33 (1H, dd, J=8.2 Hz and J=1.8 Hz), 6.76 (1H, s), 6.66 (1H, d, J=8.3 Hz), 6.57 (1H, s), 6.00 (1H, d, J=1.3 Hz), 5.95 (1H, d, J=1.3 Hz), 5.21 (1H, m), 4.05 (2H, broad s), 2.65 (2H, m), 2.47 (1H, m), 2.19 (1H, m), 2.18 (3H, s), 1.30 (3H, d, J=6.4 Hz), 1.03 (3H, t, J=7.5 Hz).			

No. of Example	Nomenclature of compound	Brutto formula	Cystallizing solvent, Mp.°C	Yield (%)
29	(±)-5-(4-amino-3-methyl-phenyl)-7-(N--cyclo-propyl-carbamoyl)-7,8-dihydro-8--methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	$C_{22}H_{24}N_4O_3$ (392.46)	diethyl ether 179-181	60
Method: B	Elementary analysis C: calc.: 67.33 (%), found: 67.29 (%); H: calc.: 6.16 (%), found: 6.13 (%); N: calc.: 14.28 (%), found: 14.10 (%)			
	^{1}H NMR ($CDCl_3$) δ 7.29 (1H, s), 7.23 (1H, dd, J=8.2 Hz and J=1.6 Hz), 6.72 (1H, s), 6.66 (1H, d, J=8.2 Hz), 6.57 (1H, s), 6.08 (1H, broad s), 5.98 (1H, s), 5.95 (1H, d, J=0.8 Hz), 5.16 (1H, m), 3.95 (2H, broad s), 2.81 (1H, dd, J=14.1 Hz and J=4.5 Hz), 2.64 (2H, m), 2.18 (3H, s), 1.15 (3H, d, J=6.3 Hz), 0.71 (2H, m), 0.51 (2H, m).			
30	(±)-5-(4-amino-3-methyl-phenyl)-7,8--dihydro-8-methyl-7-(N-methoxy--carbamoyl)-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	$C_{20}H_{22}N_4O_4$ (382.42)	ethanol 150-152	78
Method: A	Elementary analysis C: calc.: 62.82 (%), found: 62.49 (%); H: calc.: 5.80 (%), found: 5.83 (%); N: calc.: 14.65 (%), found: 14.35 (%)			
	^{1}H NMR ($CDCl_3$) δ 8,30 (1H, s), 7,26 (1H, broad s), 7,25 (1H, dd, J=8,2 Hz and J=2,2 Hz), 6,75 (1H, s), 6,67 (1H, d, J=8,4 Hz), 6,59 (1H, s), 6,01 (1H, d, J=1,5 Hz), 5,98 (1H, d, J=1,5 Hz), 5,18 (1H, m), 3,77 (3H, s), 2,70 (2H, m), 2,20 (3H, s), 1,23 (3H, d, J=6,2 Hz).			
31.	(±)-5-(4-amino-3-methyl-phenyl)-7,8--dihydro-8-methyl-7-(N-methyl-carbamoyl)--9H-1,3-dioxolo[4,5-h][2,3] benzodiazepine	$C_{20}H_{22}N_4O_3$ (366.42)	acetonitrile 177-180	72
Method: A	Elementary analysis C: calc.: 65.56 (%), found: 64.91 (%); H: calc.: 6.05 (%), found: 6.03 (%); N: calc.: 15.29 (%), found: 14.98 (%)			
	^{1}H NMR ($CDCl_3$) δ 7.34 (1H, s), 7.25 (1H, dd, J=8.2 Hz and J=2.4 Hz), 6.73 (1H, s), 6.66 (1H, d, J=8.2 Hz), 6.58 (1H, s), 5.97 (1H, d, J=1.1 Hz), 5.95 (1H, d, J=1.1 Hz), 5.87 (1H, m), 5.17 (1H, m), 3.98 (2H, broad s), 2.84 (3H, d, J=4.8 Hz), 2.81 (1H, dd, J=14.2 Hz and J=4.7 Hz), 2.64 (1H, dd, J=14.0 Hz and J=10.2 Hz), 2.18 (3H, s), 1.15 (3H, d, J=6.3 Hz).			

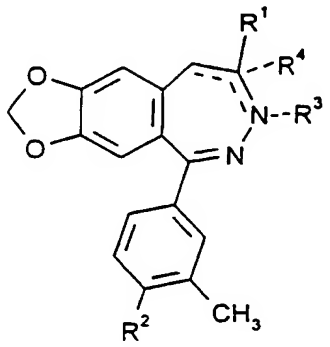
No. of Example	Nomenclature of compound	Brutto formula	Cystallizing solvent, Mp.°C	Yield (%)
32.	(±)-7-acetyl-5-(4-amino-3-methyl-phenyl)--7,8-dihydro-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine-8-carboxylic acid--amid	$C_{20}H_{20}N_4O_4$ (380.41)	acetonitrile 177-180	72
Method: A	Elementary analysis C: calc.: 63.15 (%), found: 62.30 (%); H: calc.: 5.30 (%), found: 5.05 (%); N: calc.: 14.73 (%), found: 14.29 (%)			
	^{1}H NMR ((CD$_3$))SO δ 7.30 (1H, d, J=1.3 Hz), 7.18 (1H, dd, J=8.3 Hz and J=1.9 Hz), 7.07 (2H, broad s), 6.98 (1H, s), 6.64 (1H, d, J=8.4 Hz), 6.60 (1H, s), 6.10 (1H, d, J=0.6 Hz), 6.06 (1H, s), 5.51 (2H, broad s), 5.24 (1H, dd, J=12.3 Hz and J=5.0 Hz), 3.03 (1H, dd, J=13.7 Hz and J=5.0 Hz), 2.74 (1H, t, J=13.0 Hz), 2.08 (3H, s), 2.00 (3H, s).			
33.	5-(4-amino-3-methyl-phenyl)-8-cyano-9H--1,3-dioxolo[4,5-h][2,3]benzodiazepine	$C_{18}H_{14}N_4O_2$ (318.34)	acetonitrile 252-255	54
Method: B	Elementary analysis C: calc.: 67.92 (%), found: 67.66 (%); H: calc.: 4.43 (%), found: 4.30 (%); N: calc.: 17.60 (%), found: 17.02 (%)			
	^{1}H NMR ((CD$_3$))SO δ 7,27 (1H, d, J=1,4 Hz), 7,19 (1H, s), 7,15 (1H, dd, J=8, Hz and J=1,8 Hz), 6,82 (1H, s), 6,65 (1H, d, J=8,4 Hz), 6,18 (1H, d, J=0,7 Hz), 6,12 (1H, d, J=0,7 Hz), 5,58 (2H, broad s), 3,75 (1H, d, J=13,6 Hz), 3,10 (1H, d, J=13,6 Hz), 2,08 (3H, s).			
34.	5-(4-amino-3-methyl-phenyl)-8--(semicarbazono-methyl)-9H-1,3--dioxolo[4,5-h][2,3]benzodiazepine	$C_{19}H_{18}N_6O_3$ (378.39)	acetonitrile 287-291	68
Method: A	Elementary analysis C: calc.: 60.31 (%), found: 59.82 (%); H: calc.: 4.79 (%), found: 4.67 (%); N: calc.: 22.21 (%), found: 21.45 (%)			
	^{1}H NMR (CDCl$_3$) δ 10.54 (1H, s), 7.45 (1H, s), 7.20 (2H, m), 6.82 (2H, broad s), 6.72 (1H, s), 6.64 (1H, d, J=8.7 Hz), 6.13 (1H, s), 6.03 (1H, s), 5.38 (2H, broad s), 4.42 (1H, d, J=12.5 Hz), 2.56 (1H, d, J=12.5 Hz), 2.09 (3H, s).			

No. of Example	Nomenclature of compound	Brutto formula	Cystallizing solvent, Mp.°C	Yield (%)
35.	7-acetyl-5-(4-amino-3-methyl-phenyl)-8--methyl-7H-1,3-dioxolo[4,5--h][2,3]benzodiazepine	$C_{20}H_{19}N_3O_3$ (349.39)	acetonitrile 222-223	63
Method: B	Elementary analysis C / H / N			
	calc.: 68.75 (%) / 5.48 (%) / 12.03 (%)			
	found: 68.43 (%) / 5.42 (%) / 11.80 (%)			
	^{1}H NMR ($CDCl_3$) δ 7.28 (1H, d, J=1.5 Hz), 7.13 (1H, dd, J=8.2 Hz and J=2.0 Hz), 6.73 (1H, s), 6.72 (1H, s), 6.63 (1H, d, J=8.2 Hz), 6.32 (1H, d, J=1.2 Hz), 6.03 (1H, d, J=1.1 Hz), 5.96 (1H, d, J=1.2 Hz), 3.90 (2H, broad s), 2.27 (3H, d, J=1.2 Hz), 2.23 (3H, s), 2.17 (3H, s).			
36.	5-(4-amino-3-methyl-phenyl)-7-(N-methyl--carbamoyl)-8-methyl-7H-1,3-dioxolo--[4,5-h][2,3]benzodiazepine	$C_{20}H_{20}N_4O_3$ (36441)	tert.buthyl--methyl-ether 208-209	69
Method: B	Elementary analysis C / H / N			
	calc.: 65.92 (%) / 5.53 (%) / 15.37 (%)			
	found: 65.07 (%) / 5.48 (%) / 14.81 (%)			
	^{1}H NMR ($CDCl_3$) δ 7.20 (1H, d, J=1.1 Hz), 7.10 (1H, dd, J=8.2 Hz and J=1.9 Hz), 6.66 (1H, s), 6.64 (1H, s), 6.63 (1H, d, J=8.2 Hz), 6.13 (1H, s), 6.03 (1H, q, J=4.8 Hz), 6.00 (1H, broad s), 5.94 (1H, broad s), 3.90 (2H, broad s), 2.93 (3H, d, J=4.9 Hz), 2.21 (3H, s), 2.16 (3H, s).			
37.	5-(4-amino-3-methyl-phenyl)-7-(N--cyclopropyl-carbamoyl)-8-methyl-7H-1,3-dioxolo-4,5-h][2,3]benzodiazepine	$C_{22}H_{22}N_4O_3$ (390.45)	ethanol 208-209	65
Method: B	Elementary analysis C / H / N			
	calc.: 67.68 (%) / 5.68 (%) / 14.35 (%)			
	found: 67.39 (%) / 5.69 (%) / 13.97 (%)			
	^{1}H NMR ($CDCl_3$) δ 7.15 (1H, s), 7.08 (1H, dd, J=8.4 Hz and J=2.2 Hz), 6.67 (1H, s), 6.66 (1H, d, J=8.4 Hz), 6.64 (1H, s), 6.22 (1H, s), 6.13 (1H, s), 6.01 (1H, broad s), 5.95 (1H, broad s), 3.85 (2H, broad s), 2.72 (1H, m), 2.22 (3H, d, J=1.1 Hz), 2.17 (3H, s), 0.76 (2H, m), 0.60 (2H, m).			

No. of Example	Nomenclature of compound	Brutto formula	Cystallizing solvent, Mp.°C	Yield (%)
38.	(±)-7-acetyl-5-(4-amino-3-methyl-phenyl)-8--cyano-7,8-dihydro-8-methyl--9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	$C_{21}H_{20}N_4O_3$ (376.42)	ethyl-acetate 156-158	62
Method: C	Elementary analysis C H N calc.: 67.01 (%) 5.36 (%) 14.88 (%) found: 64.39 (%) 5.55 (%) 14.42 (%)			
	^{1}H NMR ($CDCl_3$) δ 7.39 (1H, d, J=1.4 Hz), 7.30 (1H, dd, J=2.0 and 8.3 Hz), 6.96 (1H, s), 6.66 (1H, d, J=8.3 Hz), 6.64 (1H, s), 6.07 (1H, d, J=1.3 Hz), 6.01 (1H, d, J=1.3 Hz), 4.06 (2H, broad s), 3.03 (1H, d, J=14.0 Hz), 2.93 (1H, d, J=14.0 Hz), 2.18 (3H, s), 2.17 (3H, s), 1.81 (3H, s).			
39.	(±)-5-(4-amino-3-methyl-phenyl)-8-cyano--7,8-dihydro-6-methyl-7-propionyl-9H-1,3--dioxolo[4,5-h][2,3]benzodiazepine monohydrate	$C_{22}H_{22}N_4O_3 . H_2O$ (408.46)	diethyl ether 162-163	69
Method: C	Elementary analysis C H N calc.: 64.69 (%) 5.92 (%) 13.72 (%) found: 62.63 (%) 5.62 (%) 13.26 (%)			
	^{1}H NMR ($CDCl_3$) δ 7.39 (1H, s), 7.31 (1H, d, J=8.2 Hz), 6.97 (1H, s), 6.67 (1H, d, J=8.3 Hz), 6.63 (1H, s), 6.07 (1H, s), 6.01 (1H, s), 4.06 (2H, broad s), 3.03 (1H, d, J=13.9 Hz), 2.92 (1H, d, J=13.6 Hz), 2.60 (1H, m), 2.56 (1H, m), 2.19 (3H, s), 1.81 (3H, s), 1.10 (3H, t, J=7.4 Hz).			

What we claim is,

1. Compounds of the general Formula



I

(wherein

R^1 stands for methyl, formyl, carboxy, cyano, -CH=NOH, $-CH=NNHCONH_2$ or $-NR^5R^6$, wherein

R^5 and R^6 independently from each other represent hydrogen or lower alkyl or together with the nitrogen atom, they are attached to, form a 5- or 6-membered, saturated or unsaturated heterocyclic ring optionally containing one or more further nitrogen, sulfur and/or oxygen atom(s);

R^2 is nitro or amino;

R^3 stands for hydrogen, lower alkanoyl or $CO-NR^7R^8$, wherein

R^7 and R^8 independently from each other stand for hydrogen, lower alkoxy, lower alkyl or lower cycloalkyl or together with the nitrogen atom, they are attached to, form a 5- or 6--membered, saturated or unsaturated

heterocyclic ring optionally containing one or more further nitrogen, sulfur and/or oxygen atom(s);

R^4 is hydrogen or lower alkyl;

the dotted lines have the following meaning:

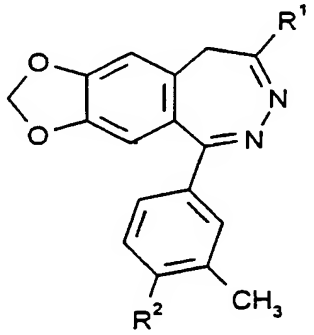
if R^3 and R^4 are not present, the bond between positions C^8 and C^9 is a single bond and the bond between positions C^8 and N^7 is a double bond;

if R^3 and R^4 are present, the bonds between positions C^8 and C^9 and between positions C^8 and N^7 are single bonds; and

if R^3 is present and R^4 is missing, the bond between positions C^8 and C^9 is a double bond and the bond between positions C^8 and N^7 is a single bond)

and pharmaceutically acceptable salts thereof.

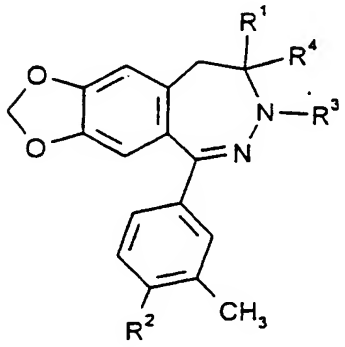
2. Compounds of the general Formula



IA

(wherein R^1 and R^2 are as stated in Claim 1) and pharmaceutically acceptable acid addition salts thereof.

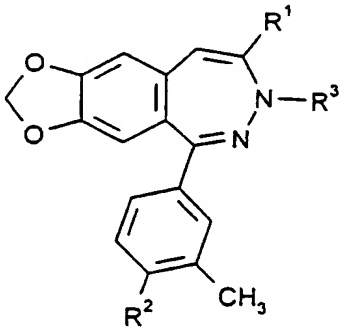
3. Compounds of the general Formula



IB

(wherein R^1, R^2, R^3 and R^4 are as stated in Claim 1) and pharmaceutically acceptable acid addition salts thereof.

4. Compounds of the general Formula



IC

(wherein R^1, R^2 and R^3 are as stated in Claim 1) and pharmaceutically acceptable acid addition salts thereof.

5. Compounds according to any of Claims 1-4 wherein R^2 is amino.

6. Compounds of the general Formula IB according to Claim 5.

7. Compounds according to Claim 6 wherein R^1 stands for methyl or cyano; R^2 is amino; R^3 represents lower alkanoyl or -$CONR^7R^8$; R^7 is hydrogen; R^8 is lower alkyl, lower

alkoxy or lower cycloalkyl and R^4 represents hydrogen or methyl.

8. The following compound according to Claim 7:
7-acetyl-5-(4-amino-3-methyl-phenyl)-7,8-dihydro-8-methyl--9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine.

9. The following compounds according to Claim 7:
5-(3-methyl-4-amino-phenyl)-7-propionyl-7,8-dihydro-8--methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-(N-cyclopropyl-carbamoyl)-7,8--dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-(N-methoxy-carbamoyl)-7,8--dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
-5-(4-amino-3-methyl-phenyl)-7-(N-methyl-carbamoyl)-7,8--dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-acetyl-8-cyano-7,8-dihydro-8--methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-8-cyano-7-propionyl-7,8-dihydro--8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine.

10. Compounds according to Claim 4 wherein R^1 is methyl; R^2 stands for amino; R^3 is lower alkanoyl or -CO--NR^7R^8; R^7 is hydrogen and R^8 represents lower alkyl, lower alkoxy or lower cycloalkyl.

11. The following compounds according to Claim 10:
7-acetyl-5-(4-amino-3-methyl-phenyl)-8-methyl-7H-1,3--dioxolo[4,5-h][2,3]benzodiazepine;
7-(N-methyl-carbamoyl)- 5-(4-amino-3-methyl-phenyl)-8--methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;

7-(N-cyclopropyl-carbamoyl)- 5-(4-amino-3-methyl-phenyl)-8--methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine.

12. Process for the preparation of compounds of the general Formula I (wherein

R^1 stands for methyl, formyl, carboxy, cyano, -CH=NOH, $-CH=NNHCONH_2$ or $-NR^5R^6$, wherein

R^5 and R^6 independently from each other represent hydrogen or lower alkyl or together with the nitrogen atom, they are attached to, form a 5- or 6-membered, saturated or unsaturated heterocyclic ring optionally containing one or more further nitrogen, sulfur and/or oxygen atom(s);

R^2 is nitro or amino;

R^3 stands for hydrogen, lower alkanoyl or $CO-NR^7R^8$, wherein

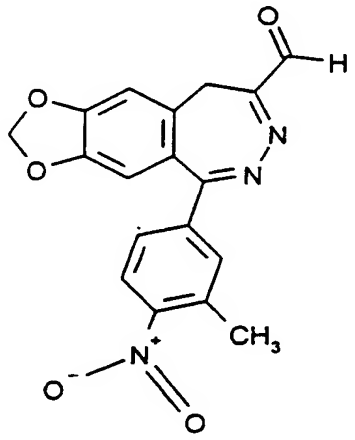
R^7 and R^8 independently from each other stand for hydrogen, lower alkoxy, lower alkyl or lower cycloalkyl or together with the nitrogen atom, they are attached to, form a 5- or 6--membered, saturated or unsaturated heterocyclic ring optionally containing one or more further nitrogen, sulfur and/or oxygen atom(s);

R^4 is hydrogen or lower alkyl;

the dotted lines have the following meaning:

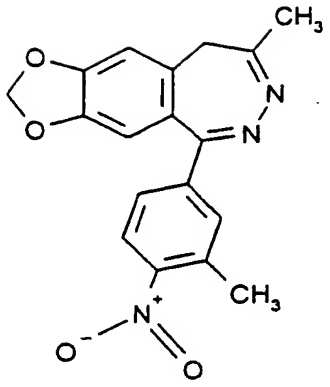
if R^3 and R^4 are not present, the bond between positions C^8 and C^9 is a single bond and the bond between positions C^8 and N^7 is a double bond;
if R^3 and R^4 are present, the bonds between positions C^8 and C^9 and between positions C^8 and N^7 are single bonds; and
if R^3 is present and R^4 is missing, the bond between positions C^8 and C^9 is a double bond and the bond between positions C^8 and N^7 is a single bond)
and pharmaceutically acceptable acid addition salts thereof which comprises

a) for the preparation of 8-formyl-5-(3-methyl-4-nitro--phenyl)-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine of the Formula



III

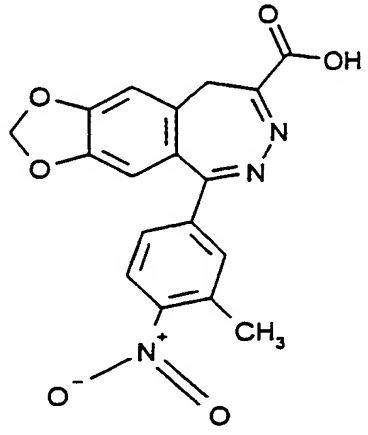
III, oxidizing 8-methyl-5-(4-nitro-3-methyl-phenyl)-9H-1,3--dioxolo[4,5-h][2,3]benzodiazepine of the Formula



II

or

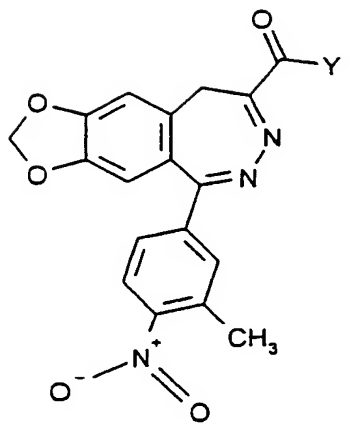
b) for the preparation of 5-(3-methyl-4-nitro-phenyl)--9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-8-carboxylic acid of the Formula



IV

oxidizing 8-formyl-5-(3-methyl-4-nitro-phenyl)-9H-1,3--dioxolo[4,5-h][2,3]benzodiazepine of the Formula III; or

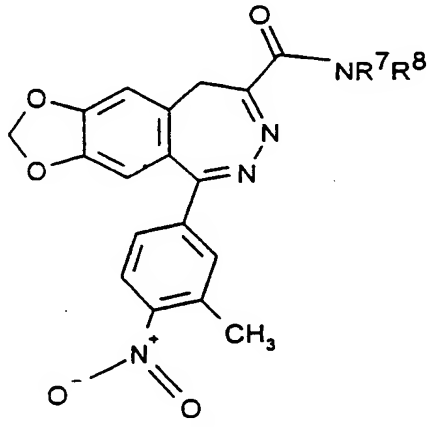
c) for the preparation of compounds of the general Formula



V

(wherein Y stands for a leaving group), reacting the compound of the Formula IV with a compound capable of introducing group Y; or

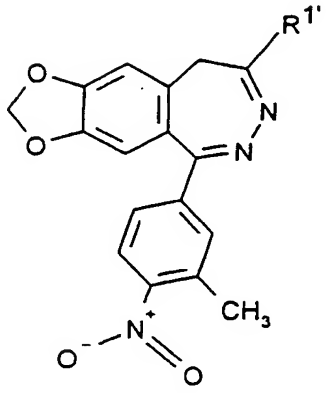
d) for the preparation of the compound of the general Formula



VI

(wherein R^7 and R^8 are as stated above), reacting the carboxylic acid of the Formula IV or a reactive derivative thereof of the Formula V with an amine of the general Formula HNR^7R^8; or

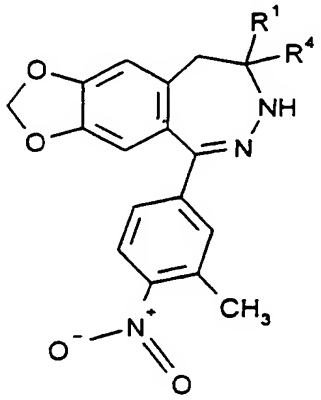
e) for the preparation of compounds of the general Formula



VII

(wherein $R^{1'}$ stands for cyano, -CH=NOH or -CH=NNHCONH$_2$), converting in the compound of the Formula III the formyl group into an $R^{1'}$ group; or

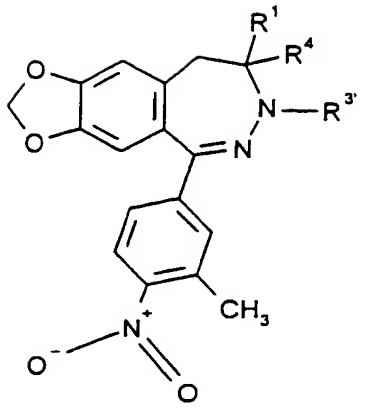
f) for the preparation of compounds of the general Formula



VIII

(wherein R^1 and R^4 are as stated above), saturating the C^8-N^7 double bond by addition or reduction; or

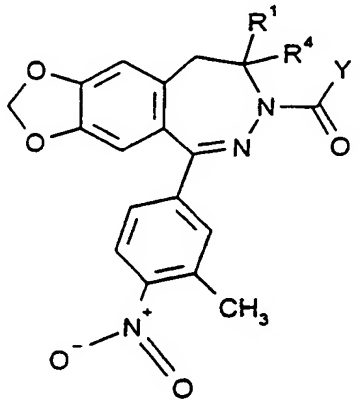
g) for the preparation of compounds of the general Formula



IX

(wherein $R^{3'}$ is lower alkanoyl), reacting a compound of the general Formula VIII with a compound capable of introducing a lower alkanoyl group; or

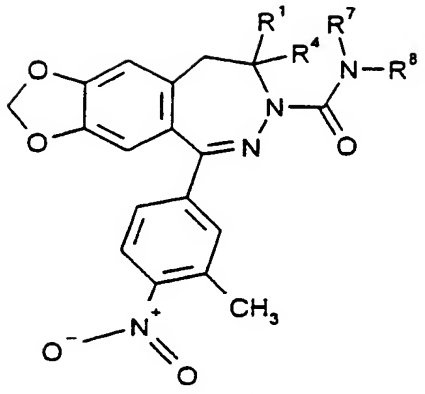
h) for the preparation of compounds of the general Formula



X

(wherein Y is a leaving group and R^1 and R^4 are as stated above), reacting a compound of the general Formula VIII with a compound capable of introducing the -COY group; or

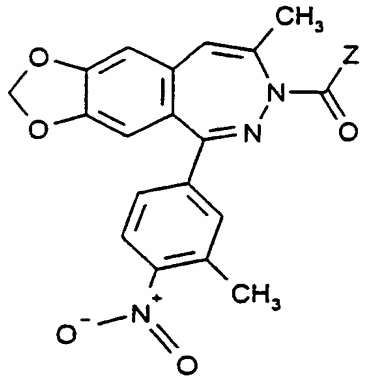
i) for the preparation of compounds of the general Formula



XI

(wherein R^1, R^4, R^7 and R^8 are as stated above), reacting a compound of the general Formula X or the corresponding free carboxylic acid with an amine of the general Formula HNR^7R^8; or

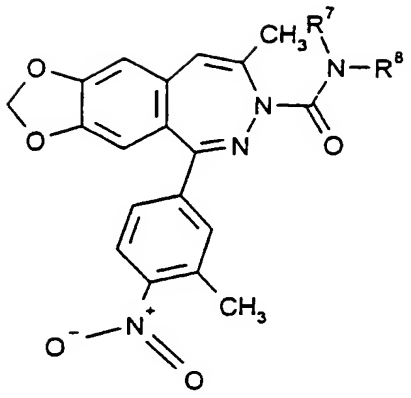
j) for the preparation of compounds of the general Formula



XII

(wherein Z stands for a leaving group), reacting the compound of the Formula II with a compound capable of introducing the -COZ group; or

k) for the preparation of compounds of the general Formula



XIII

(wherein R^7 and R^8 are as stated above), reacting a compound of the general Formula XII with an amine of the general Formula HNR^7R^8; or

I) for the preparation of compounds of the general Formula I, wherein R^2 stands for amino, reducing the corresponding compound of the general Formula I, wherein R^2 is nitro;

and, if desired, converting a compound of the general Formula I into a pharmaceutically acceptable acid addition salt thereof or setting free a compound of the general Formula I from a salt.

13. Process according to process I) of Claim 12 which comprises reducing a compound of the general Formula II, VII, IX, XI, XII or XIII.

14. Process according to Claim 13 which comprises carrying out reduction by using stannous(II)chloride, sodium dithionite or by means of catalytic hydrogenation.

15. Process according to Claim 14 which comprises using a Raney-nickel, palladium or platinum catalyst, and as

hydrogen source hydrogen, hydrazine, hydrazine hydrate, formic acid, trialkyl ammonium formate or an alkali formate.

16. Pharmaceutical composition which comprises as active ingredient a compound of the general Formula I (wherein

R^1 stands for methyl, formyl, carboxy, cyano, -CH=NOH, $-CH=NNHCONH_2$ or $-NR^5R^6$, wherein

R^5 and R^6 independently from each other represent hydrogen or lower alkyl or together with the nitrogen atom, they are attached to, form a 5- or 6-membered, saturated or unsaturated heterocyclic ring optionally containing one or more further nitrogen, sulfur and/or oxygen atom(s);

R^2 is nitro or amino;

R^3 stands for hydrogen, lower alkanoyl or $CO-NR^7R^8$, wherein

R^7 and R^8 independently from each other stand for hydrogen, lower alkoxy, lower alkyl or lower cycloalkyl or together with the nitrogen atom, they are attached to, form a 5- or 6--membered, saturated or unsaturated heterocyclic ring optionally containing one or more further nitrogen, sulfur and/or oxygen atom(s);

R^4 is hydrogen or lower alkyl;

the dotted lines have the following meaning:

if R^3 and R^4 are not present, the bond between positions C^8 and C^9 is a single bond and the bond between positions C^8 and N^7 is a double bond;
if R^3 and R^4 are present, the bonds between positions C^8 and C^9 and between positions C^8 and N^7 are single bonds; and
if R^3 is present and R^4 is missing, the bond between positions C^8 and C^9 is a double bond and the bond between positions C^8 and N^7 is a single bond)
or a pharmaceutically acceptable acid addition salt thereof.

17. Pharmaceutical composition according to Claim 16 which comprises as active ingredient a compound of the general Formula I wherein R^2 is amino.

18. Pharmaceutical composition according to Claim 17 which comprises as active ingredient a compound of the general Formula IB.

19. Pharmaceutical composition according to Claim 18 which comprises as active ingredient a compound of the general Formula IB, wherein R^1 stands for methyl or cyano; R^2 is amino; R^3 represents lower alkanoyl or $-CONR^7R^8$; R^7 is hydrogen; R^8 is lower alkyl, lower alkoxy or lower cycloalkyl and R^4 represents hydrogen or methyl.

20. Pharmaceutical composition according to Claim 19 which comprises as active ingredient 7-acetyl-5-(4-amino-3--methyl-phenyl)-7,8-dihydro-8-methyl-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine.

21. Pharmaceutical composition according to Claim 19 which comprises as active ingredient 5-(3-methyl-4-amino-

-phenyl)-7-propionyl-7,8-dihydro-8-methyl-9H-1,3-dioxolo[4,5-
-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-(N-cyclopropyl-carbamoyl)-7,8-
-dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-(N-methoxy-carbamoyl)-7,8-
-dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-(N-methyl-carbamoyl)-7,8-
-dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-acetyl-8-cyano-7,8-dihydro-8-
-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-8-cyano-7-propionyl-7,8-dihydro-
-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine.

22. Pharmaceutical composition according to Claim 16 which comprises as active ingredient a compound of the general Formula IC wherein R^1 is methyl; R^2 stands for amino; R^3 is lower alkanoyl or -CO-NR^7R^8; R^7 is hydrogen and R^8 represents lower alkyl, lower alkoxy or lower cycloalkyl.

23. Pharmaceutical composition according to Claim 22 which comprises as active ingredient
7-acetyl-5-(4-amino-3-methyl-phenyl)-8-methyl-7H-1,3-
-dioxolo[4,5-h][2,3]benzodiazepine;
7-(N-methyl-carbamoyl)- 5-(4-amino-3-methyl-phenyl)-8-
-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
7-(N-cyclopropyl-carbamoyl)- 5-(4-amino-3-methyl-phenyl)-8-
-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine.

24. Pharmaceutical compositions having neuroprotective effect, useful in the treatment of symptoms

accompanied by all kinds of acute and chronical neurodegeneration, especially Parkinson disease, Alzheimer disease, amyotropic lateral sclerosis, stroke, acute head injuries, epilepsy, against spasms, alleviation of pain, to influence vomitting, schisophreny, migraine, urination problems, as anxyolitics, against drug addiction and to alleviate the symptoms of Parkinsonism.

25. Process for the preparation of pharmaceutical compositions according to Claims 16-23 which comprises admixing a compound of the general Formula I or a pharmaceutically acceptable acid addition salt thereof with inert solid or liquid pharmaceutical carriers and bringing the mixture to a galenic form.

26. Use of compounds of the general Formula I and pharmaceutically acceptable acid addition salts thereof for the preparation of pharmaceutical compositions having neuroprotective effect, useful in the treatment of symptoms accompanied by all kinds of acute and chronical neurodegeneration, especially Parkinson disease, Alzheimer disease, amyotropic lateral sclerosis, stroke, acute head injuries, epilepsy, against spasms, alleviation of pain, to influence vomitting, schisophreny, migraine, urination problems, as anxyolitics, against drug addiction and to alleviate the symptoms of Parkinsonism.

27. Method of treatment of diseases according to Claim 26 which comprises administering to a patient in need of such treatment a pharmaceutically effective amount of a

compound of the general Formula I or a pharmaceutically acceptable acid addition salt thereof.

— • —

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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18 January 2001 (18.01.2001)

PCT

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(21) International Application Number: PCT/HU00/00074

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P 9902291 7 July 1999 (07.07.1999) HU

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(74) Agent: **ADVOPATENT**; Office of Patent and Trademark Attorneys, P.O. Box 11, H-1251 Budapest (HU).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

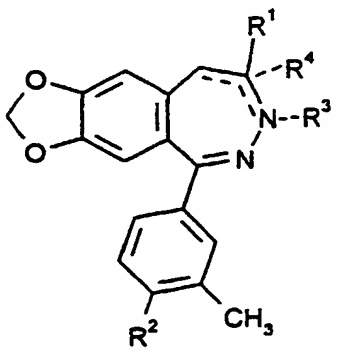
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(88) Date of publication of the international search report: 10 May 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW 2,3-BENZODIAZEPINE DERIVATIVES



(I)

(57) Abstract: The invention relates to new 2,3-benzodiazepine derivatives of general Formula (I), (wherein R^1 stands for methyl, formyl, carboxy, cyano, -CH=NOH, -CH=NNHCONH$_2$ or -NR^{5}R^6, wherein R^5 and R^6 independently from each other represent hydrogen or lower alkyl or together with the nitrogen atom, they are attached to, form a 5- or 6-membered, saturated or unsaturated heterocyclic ring optionally containing one or more further nitrogen, sulfur and/or oxygen atom(s); R^2 is nitro or amino; R^3 stands for hydrogen, lower alkanoyl or CO-NR^{7}R^8, wherein R^7 and R^8 independently from each other stand for hydrogen, lower alkoxy, lower alkyl or lower cycloalkyl or together with the nitrogen atom, they are attached to, form a 5- or 6-membered, saturated or unsaturated heterocyclic ring optionally containing ne or more further nitrogen, sulfur and/or oxygen atom(s); R^4 is hydrogen r lower alkyl; the dotted lines have the following meaning: if R^3 and R^4 are not present, the bond between positions C^8 and C^9 is a single bond and the bond between positions C^8 and N^7 is a double bond; if R^3 and R^4 are present, the bonds between positions C^8 and C^9 and between positi n C^8 and N^7 are single bonds; and if R^3 is present and R^4 is missing, the bond between positions C^8 and C^9 is a double bond and the bond between positions C^8 and N^7 is a single bond) and salts thereof. The invention compounds have neuroprotective effect.

WO 01/04122 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 00/00074

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D491/04 A61K31/551 A61P25/00 //(C07D491/04,317:00, 243:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 07707 A (EGIS GYOGYSZERGYAR RT) 18 February 1999 (1999-02-18) the whole document	1-27
Y	WO 92 11262 A (GYOGYSRERKUTATO INTEZET K.V.) 9 July 1992 (1992-07-09) the whole document	1-27
Y	WO 97 34878 A (COCENSYS, INC.) 25 September 1997 (1997-09-25) the whole document	1-27
Y	EP 0 492 485 A (GYOGYSZERKUTATO INTEZET) 1 July 1992 (1992-07-01) the whole document	1-27

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2001	30/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Beslier, L

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 00/00074

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 01357 A (GYOGYSZERKUTATO INTEZET KFT.) 12 January 1995 (1995-01-12) the whole document	1-27

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU 00/00074

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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22096

PATENT COOPERATION TREATY

2001 APR 17.

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INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
ADVOPATENT Office of Patent and
Trademark Attorneys
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H-1251 Budapest
HONGRIE

PCT

WRITTEN OPINION

(PCT Rule 66)

2001. 07. 12.

Date of mailing *(day/month/year)*	12.04.2001
Applicant's or agent's file reference: 14704 KB	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/HU00/00074	04/07/2000	07/07/1999

International Patent Classification (IPC) or both national classification and IPC
C07D491/04

Applicant
EGIS GYOGYSZERGYAR RT. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 07/11/2001.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Stroeter, T

Formalities officer (incl. extension of time limits)
Brell, S
Telephone No. +49 89 2399 7271

14770

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, pages:

1-61 as originally filed

Claims, No.:

1-27 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 27,

because:

   ☒ the said international application, or the said claims Nos. 27 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	24
Inventive step (IS)	Claims	
Industrial applicability (IA)	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 27 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Prior art documents

Reference is made to the following documents which mention 1,3-dioxolo-2,3-benzodiazepine derivatives. The given numbering will be adhered to in the rest of the procedure:

D1: WO 99 07707 A (EGIS GYOGYSZERGYAR RT)
D2: WO 92 11262 A (GYOGYSRERKUTATO INTEZET K.V.)
D3: WO 97 34878 A (COCENSYS, INC.)
D4: EP-A-0 492 485 (GYOGYSZERKUTATO INTEZET)
D5: WO 95 01357 A (GYOGYSZERKUTATO INTEZET KFT.)

2 Novelty (Article 33(2) PCT) and Inventive step (Article 33(3) PCT)

2.1 Claims 1-23 and 25-27:

Article 33(2) PCT: The group of compounds as claimed in present claim 1 (as well as in dependent claims 2 to 11) is novel over the compounds disclosed in D1 to D5 due to the presence of a methyl group in 3-position (and as such in o-position to the amino group or NO_2 group, respectively) of the phenyl ring.

Article 33(3) PCT: Document D4 names in examples 15-25 some structurally related neuroprotective agents which (partly) act according to D2, page 4, 2nd paragraph, as antagonists of AMPA receptors.

By revealing the present compounds of formula (I), the present application gives a non-obvious solution to the problem of how to provide AMPA receptor antagonists having an improved neuroprotective activity, i.e. a lower PD_{50} value compared to the closest prior art compounds of D4. The presence of the methyl group as stated above leads to a slower N-acetylation of the neighbouring amino group (this reaction is an undesired metabolic effect since it leads to less active compounds) as was made credible via the comparative data given on present pages 28-30. As a consequence the sterically hindered compounds have a better neuroprotective effect than those having no methyl group in 3-position as shown in the table on present page 32. Thus, the presently claimed compounds have an advantageous effect over the closest prior art compounds and are therefore involving an inventive step.

Consequently, present claims 1-11 and claims 12-23 and 25-27 which refer directly or indirectly to the compounds of present formula I are novel and inventive according to Articles 33(2) and (3) PCT.

2.2 Claim 24:

This claim is not novel, since pharmaceutical compositions providing neuroprotective effects and which are useful in the treatment of symptoms as stated in said claim are known from D1 to D5, which refer to compositions comprising compounds having a similar activity, e.g. D3, claim 17.
Please also note item **VIII**.(1).

3 Industrial applicability (Article 33(4) PCT)

The subject-matter of the present claims 1 to 26 is in accordance with the requirements of Article 33(4) PCT.

For the assessment of the present **claim 27** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

For all prior art compounds A to F wherein X=H (pages 28-30 of the present description) a reference should be given in order to fulfil the requirements of Rule 5.1(a)(ii) PCT, since these compounds are considered to form part of the closest prior art.

Re Item VIII

Certain observations on the international application

The claims have to be clear in order to meet the requirements of Article 6 PCT. Therefore the Applicant is requested to verify the following items:

(1) Present **claim 24** drawn to pharmaceutical compositions is not defined via technical features but only refers to certain effects of said compositions and as such is defined by the result to be achieved. Furthermore, said claim is not supported by the present description.

(2) In the present application **claim 27** was assigned to be dependent on claim 26. This stated dependency is not correct, because claim 27 is drawn to a method whereas claim 26 is a use claim.

(3) Present **claims 2, 3 and 4** should be formulated as dependent claims by insertion of "according to claim 1" after "compounds" in said claims.

22096

In re the Application of:	EGIS Gyógyszergyár Rt.
International Appln. No.:	PCT/HU00/00074
International Filing Date:	04/07/2000
Title:	NEW 2,3-BENZODIAZEPINE DERIVATIVES
Agent's file reference:	**14704 KB**

By fax and DHL courier

To.: EUROPEAN PATENT OFFICE
D-80298 Munich

PCT CHAPTER II
MU DG 2

Attn.: STROETER, T. Esq.

RESPONSE TO WRITTEN OPINION

Dear Sir,

This response is to the Written Opinion of the International Preliminary Examining Authority, mailed 12. April 2001, and having a reply due date of 12. July 2001.

It is acknowledged that the Examiner accepted the novelty and inventive character of the submitted claims 1 to 11 and claims 12 to 23 and 25 to 27 which refer directly or indirectly to the compounds of the Formula I.

In order to comply with the requirements and eliminating objection under D_1 to D_5 especially Claim 24 has been amended. Please replace pages 76 to 78 by amended pages 76 to 78 containing amended claims 24 and 27. The active ingredient of the general Formula (I) has been inserted into Claim 24, supported by the description page 21 line 3 from below to page 22 line 9. It is acknowledged that relating to the method of treatment a unified criteria does not exist in the PCT, however, we wish to keep Claim 27 to evaluate its admissability in the national phase. Claim 27 has been transformed into an independent claim. Similarly please replace pages 63 and 64 by amended pages 63 and 64 which contain claims 2 to 4 in a re-formulated form making them dependent from claim 1 inserting of the phrase "according to claim 1".

In the description please replace page 29 by "amended page 29. Old page 29 showed Compound D erroneously, because the 2 nitrogen atoms of the 2,3-benzodiazepine ring were missing. This obvious error has been corrected to show a correct compound D.

In the description page 3 has been replaced and completed by amended pages 3, 3a, 3b, 3c to eliminate certain defects of the application objected under Item VII. All prior art compounds A to F wherein X = H have been considered as a reference in the state of art part of the description to show the closest prior art. The elimination of said defects made necessary to complete the description with new pages 3, 3a, 3b, 3c.

Based on the discussion above and the replaced pages a favourable opinion of the Examiner is respectfully requested.

Dated: Budapest, June 27, 2001

Enclosures

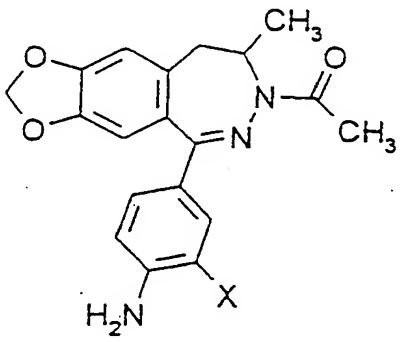
Respectfully submitted,

Béla Karácsonyi
Patent Attorney for Applicant

The therapeutical use of 2,3-benzodiazepines which exhibit a non-competitive antagonist effect on the AMPA/cainate receptor is manifold. The 2,3-benzodiazepines synthetized by research chemists of our company can be used as neuroprotective agents in case of symptoms accompanied by all types of acute and chronical neurodegeneration (e.g. Parkinson disease, Alzheimer disease, amyotropic lateral sclerosis, stroke, acute head injuries etc.). In addition to the above applications 2,3--benzodiazepines having AMPA/cainate antagonistic effect can also be used for the treatment of further symptoms, such as epilepsy, as spasmolytics, analgesics, antiemetic agents, against schizophreny, migraine, urination problems, as anxiolytics, against drug addiction, to alleviate the symptoms of Parkinsonism etc. [I. Tarnawa and E. S. Vizi, Restorative Neurol. Neurosci. 13, 41-57, (1998)].

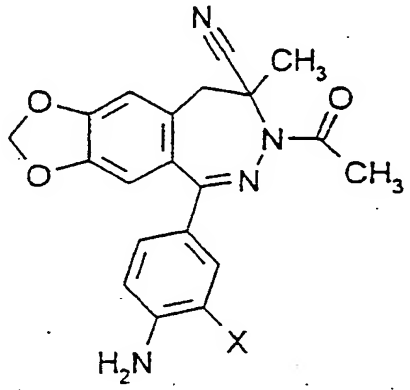
The following references of prior art compounds A to F are listed:

Compound A X = H



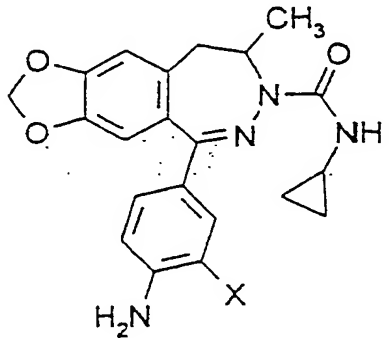
Vizi, E.S., Mike, A., Tarnawa, I.: 2,3-Benzodiazepines (GYKI-52466 and analogs): negative allosteric modulators of AMPA receptors. CNS Drug Reviews, 1996, 2, 91-126.
Tarnawa, I., Vizi, E. S.: 2,3-Benzodiazepine AMPA antagonists. Restorative Neurology and Neuroscience, 1998, 13, 41-57.

Compound B X = H



PCT WO 99/07707, 08/07/1998.

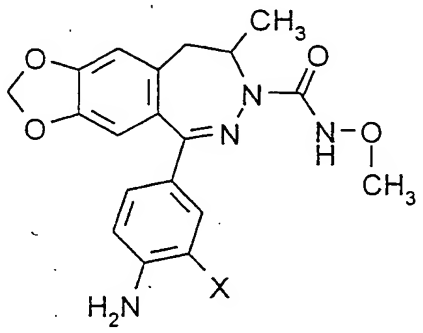
Compound C X = H



PCT WO 99/07708, 08/07/1998

Levay, G., Simo, A., Barkoczy, J., Tihanyi, K., Vegh, M., Gigler, G.: EGIS-9637, a novel antiischaemic drug exerts complex neuroprotective properties. Soc. Neurosci. Abstr. 234.13., 1999.

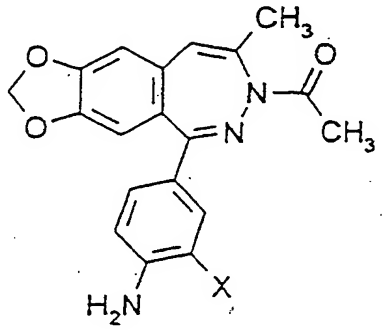
Compound D X = H



Vizi, E. S., Mike, A., Tarnawa, I.: 2,3-Benzodiazepines (GYKI-52466 and analogs): negative allosteric modulators of AMPA receptors. CNS Drug Reviews, 1996, 2, 91-126.

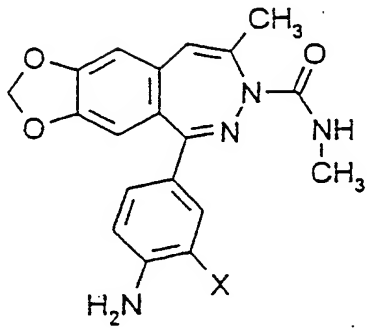
Tarnawa, I., Vizi, E.S.: 2,3-Benzodiazepine AMPA antagonists. Restorative Neurology and Neuroscience, 1998, 13, 41-57.

Compound E X = H



PCT WO 9604283A1, 07/28/1995

Compound F X = H



PCT WO 9604283A1, 07/28/1995

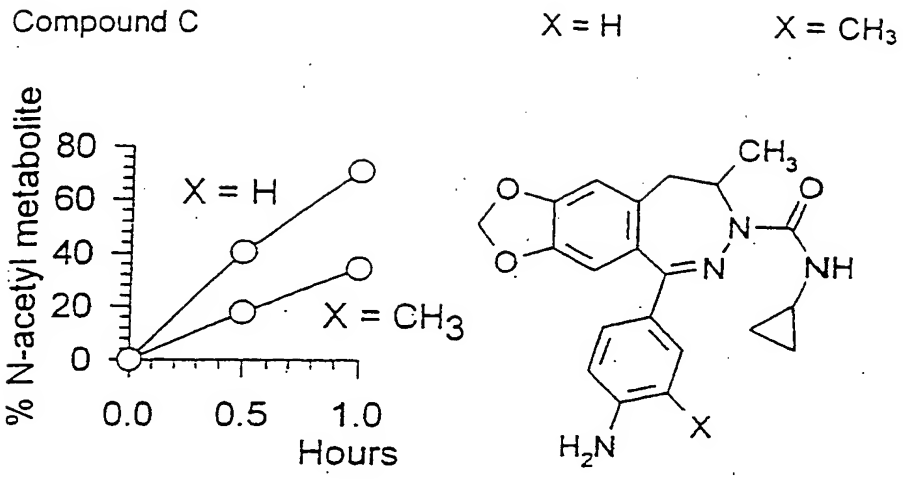
DESCRIPTION OF THE INVENTION

It is the object of the present invention to provide new 2,3-benzodiazepine derivatives having favourable biological properties.

The above object is solved by the present invention.

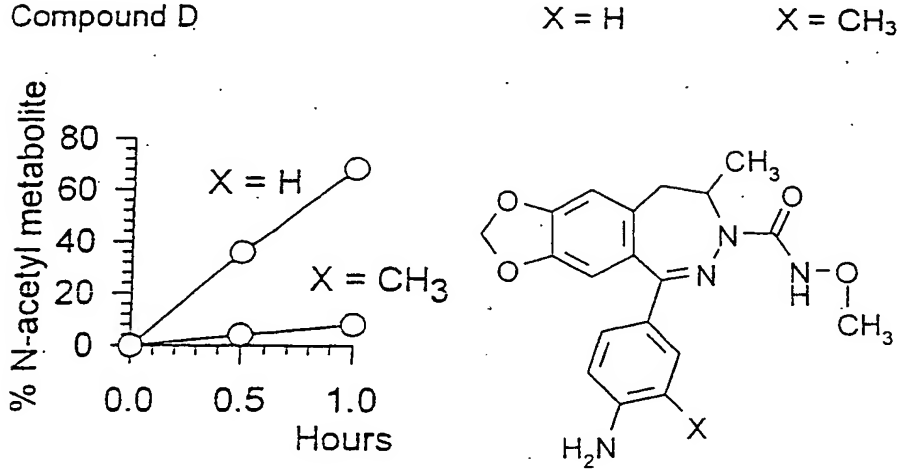
According to the present invention there are provided new compounds of the general Formula

Compound C



(Example 29)

Compound D



(Example 30)

heterocyclic ring optionally containing one or more further nitrogen, sulfur and/or oxygen atom(s);

R^4 is hydrogen or lower alkyl;

the dotted lines have the following meaning:

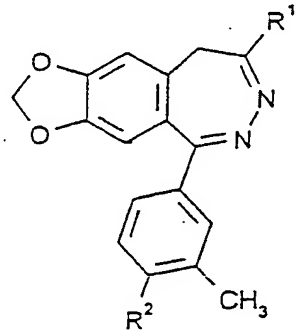
if R^3 and R^4 are not present, the bond between positions C^8 and C^9 is a single bond and the bond between positions C^8 and N^7 is a double bond;

if R^3 and R^4 are present, the bonds between positions C^8 and C^9 and between positions C^8 and N^7 are single bonds; and

if R^3 is present and R^4 is missing, the bond between positions C^8 and C^9 is a double bond and the bond between positions C^8 and N^7 is a single bond)

and pharmaceutically acceptable salts thereof.

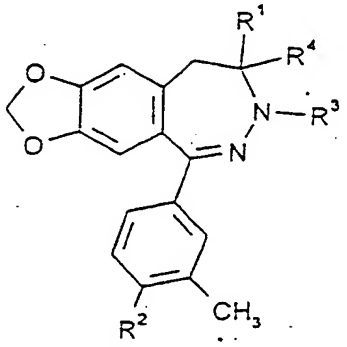
2. Compounds according to claim 1 of the general Formula



IA

(wherein R^1 and R^2 are as stated in Claim 1) and pharmaceutically acceptable acid addition salts thereof.

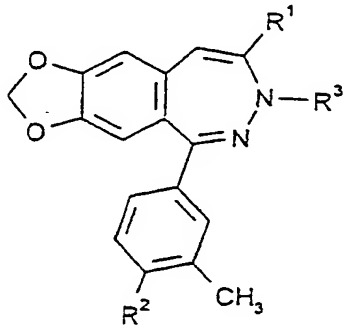
3. Compounds according to claim 1 of the general Formula



IB

(wherein R^1, R^2, R^3 and R^4 are as stated in Claim 1) and pharmaceutically acceptable acid addition salts thereof.

4. Compounds according to claim 1 of the general Formula



IC

(wherein R^1, R^2 and R^3 are as stated in Claim 1) and pharmaceutically acceptable acid addition salts thereof.

5. Compounds according to any of Claims 1-4 wherein R^2 is amino.

6. Compounds of the general Formula IB according to Claim 5.

7. Compounds according to Claim 6 wherein R^1 stands for methyl or cyano; R^2 is amino; R^3 represents lower alkanoyl or $-CONR^7R^8$; R^7 is hydrogen; R^8 is lower alkyl, lower

-phenyl)-7-propionyl-7,8-dihydro-8-methyl-9H-1,3-dioxolo[4,5--h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-(N-cyclopropyl-carbamoyl)-7,8--dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-(N-methoxy-carbamoyl)-7,8--dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-(N-methyl-carbamoyl)-7,8--dihydro-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-7-acetyl-8-cyano-7,8-dihydro-8--methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
5-(4-amino-3-methyl-phenyl)-8-cyano-7-propionyl-7,8-dihydro--8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine.

22. Pharmaceutical composition according to Claim 16 which comprises as active ingredient a compound of the general Formula IC wherein R^1 is methyl; R^2 stands for amino; R^3 is lower alkanoyl or -CO-NR^7R^8; R^7 is hydrogen and R^8 represents lower alkyl, lower alkoxy or lower cycloalkyl.

23. Pharmaceutical composition according to Claim 22 which comprises as active ingredient
7-acetyl-5-(4-amino-3-methyl-phenyl)-8-methyl-7H-1,3--dioxolo[4,5-h][2,3]benzodiazepine;
7-(N-methyl-carbamoyl)- 5-(4-amino-3-methyl-phenyl)-8--methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine;
7-(N-cyclopropyl-carbamoyl)- 5-(4-amino-3-methyl-phenyl)-8--methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine.

24. Pharmaceutical compositions according to claim 16 containing as active ingredient a compound of the general

Formula I as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof having neuroprotective effect, useful in the treatment of symptoms accompanied by all kinds of acute and chronical neurodegeneration, especially Parkinson disease, Alzheimer disease, amyotropic lateral sclerosis, stroke, acute head injuries, epilepsy, against spasms, alleviation of pain, to influence vomitting, schisophreny, migraine, urination problems, as anxyolitics, against drug addiction and to alleviate the symptoms of Parkinsonism.

25. Process for the preparation of pharmaceutical compositions according to Claims 16-23 which comprises admixing a compound of the general Formula I or a pharmaceutically acceptable acid addition salt thereof with inert solid or liquid pharmaceutical carriers and bringing the mixture to a galenic form.

26. Use of compounds of the general Formula I and pharmaceutically acceptable acid addition salts thereof for the preparation of pharmaceutical compositions having neuroprotective effect, useful in the treatment of symptoms accompanied by all kinds of acute and chronical neurodegeneration, especially Parkinson disease, Alzheimer disease, amyotropic lateral sclerosis, stroke, acute head injuries, epilepsy, against spasms, alleviation of pain, to influence vomitting, schisophreny, migraine, urination problems, as anxyolitics, against drug addiction and to alleviate the symptoms of Parkinsonism.

27. Method of treatment of symptoms accompanied by all kinds of acute and chronical neurodegeneration, espècially Parkinson disease, Alzheimer disease, amyotropic lateral sclerosis, stroke, acute head injuries, epilepsy, against spasms, alleviation of pain, to influence vomitting, schisophreny, migraine, urination problems, as anxyolitics, against drug addiction and to alleviate the symptoms of Parkinsonism, which comprises administering to a patient in need of such treatment a pharmaceutically effective amount of a compound of the general Formula I or a pharmaceutically acceptable acid addition salt thereof.

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